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SPEECHES, ARTICLES, AND SELECTED PAPERS

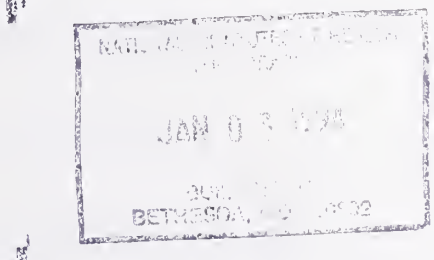
By

James B. Wyngaarden, M.D.

1982-1988

Volume 2 (of 5)

(April 22, 1983—December 12, 1984)



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Speeches, Articles, and Selected Papers
James B. Wyngaarden, M.D.

1982-1988
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CREATIVITY IN SCIENCE*

by

James B. Wyngaarden, M.D.**

I appreciate very much your gracious invitation to address the 24th Annual National Student Research Forum. I bring you greetings from your former Dean, Dr. Edward N. Brandt, Jr., now Assistant Secretary for Health, to whom I report directly. I understand he had served as faculty advisor to the National Student Research Forum for some eight years. He has told me how effective this Forum has been in encouraging bright medical students to enter research careers. In appearing here today I am doing something that I have looked forward to with real pleasure. But before embarking upon my prepared address, I want to tell your group about an exciting discovery recently made at the NIH on the mechanism of hibernation. It seems that in the fall, the bears line up in order of height and size, and head single file for the nearest cave. The smallest bear enters first, followed by the next larger, and the next, and so on until the largest bear of all enters the cave, stands up in the entranceway, obliterating all the light, and says, "First slide please." That story is by way of announcing that I will have no slides to show since this talk is scheduled immediately after lunch.

My pleasure in being here today is in part occasioned by a warm glow of nostalgia. Prior to coming to my present position about a year ago, my entire professional career had been devoted to academic medicine and biomedical research, with a heavy emphasis upon research training at student and house

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*The Dr. Benedict E. Abreu Memorial Lecture, 24th Annual National Student Forum, Galveston, Texas, on April 22, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

staff levels. I am mindful of the special honor and privilege your invitation represents, for this is indeed a unique assembly. Special tribute is due the small group of medical students who originated the idea of the Forum back in 1959, to the faculty members who recognized the merit of their plans, and particularly to Dr. Benedict E. Abreu, whose special efforts had much to do with the growth of the Forum from a regional activity to a truly national assembly.

Since becoming Director of the National Institutes of Health, I have become even more strongly convinced than before of the vital importance of attracting the ablest and brightest to careers in research, especially the need to interest and hold young men and women who are trained as physicians. Fortunately, the supply of Ph.D. scientists has held up well, but the production of physician-scientists is widely viewed as below desirable levels. In my statements to top officials in the Administration, to the Congress, and to the public, the need has been a recurrent theme, and I plan to continue that emphasis.

We are in the midst of our annual budget hearings before the House Committee on Appropriations. My colleagues and I appeared Tuesday, Wednesday, and Thursday of this week and we are scheduled to meet with the Committee again for two days next week. An important element of our testimony is the response to an instruction by the Appropriations Committee following last year's budget hearings. Let me quote from the report:

> The Committee shares the concerns that have been expressed by official and public witnesses about the difficulty of recruiting and retaining physicians for research careers, especially as all clinical research involving human patients must be done by, or at least under the guidance of, a qualified physician. It is apparent and understandable that young physicians considering health careers are often dissuaded from applying for research training or research fellowships by their perception of

instability in the federal commitment to research and by their awareness that a research career represents a substantial sacrifice when compared with almost any form of medical practice. The Committee would like NIH to review this problem carefully and to suggest what steps might usefully be taken to increase the number of young physicians who will apply for research training and to retain those who do embark on research careers."

The concerns expressed by the House Committee about the need to recruit and retain the ablest and best young physicians in research careers were important policy considerations throughout the process of development of the budget we are now defending.

While it is true that a career in research could represent a sacrifice, I think this group more than most would appreciate the wisdom of a statement made last fall by Dean John Bernard Henry of Georgetown University School of Medicine when he spoke to the entering freshman class. Let me repeat a portion of it.

He said, "The laboratory seldom seems to beckon with the same drama and excitement as the hospital, but let me assure you it is there. The laboratory and the classroom are the parents of medicine. It could not have been born without them.

"All that this profession is and has become is based on investigation and research. Someone, somewhere, sometime had an inquiring mind and the intelligence and stick-to-it-iveness to labor long hours with one goal in mind: discovery. And it is their discoveries and their accomplishments that enable us to treat our patients and exercise our profession. We would have no knowledge to impart had someone not investigated."

A second major element of my testimony concerns the momentum of science. Never before has excitement seemed so intense or the promise so

great for spectacular achievements against major diseases that afflict mankind. A well-conceived emphasis on maintaining a productive community of basic scientists has paid off in terms of the store of fundamental knowledge now at hand. The knowledge accrued in just the last ten years in virology, molecular biology, pharmacology, cell biology, and immunology opens up infinite opportunities for applications to clinical problems. Continued research on hybridomas, recombinant DNA technology, and oncogenes, for example, will soon need for further advancement the input of more clinical investigators.

My topic today, however, relates directly to the process of discovery itself. The title of this address is "Creativity in Science."

Creativity is not easy to define. The dictionary lists such synonyms as originality, inventiveness, productivity, ingenuity, and novelty. These terms imply new insights, new associations, relationships and interpretations. They imply discovery plus integration into a larger body of knowledge, the evolution of new perceptions, perhaps of new paradigms. For those who are not acquainted with the book I recommend Thomas Kuhn's The Structure of Scientific Revolutions, in which he develops the theme that science grows not by continuous, smooth expansion, but rather by the development of new paradigms, new insights that give rise to new operational tenets that give new directions to emerging fields.

Just last week there was a celebration of the 30th anniversary of the celebrated publication by Watson and Crick of a suggested structure for DNA, surely one of the greatest discoveries in biological science of all time. This new paradigm may quite plausibly be credited with inaugurating the biological revolution which is gathering momentum and progressively invading previously separate fields of biological inquiry. This revolution has led to the confluence of previously separate scientific disciplines, and as a result

such segmented fields as anatomy, physiology, pharmacology, microbiology, biochemistry, and pathology now share a common scientific base reflected in the relatedness of virtually all current scientific inquiry: the genetic control of structure, development, and function.

But let me take you back a bit to the pre-Watson-Crick days. While on the one hand I envy you your vast scientific opportunities and the array of concepts and methods awaiting your exploitation, on the other I am happy to have entered the scene when I did, to have been able to see the revolution unfold, and to have played a small part in it.

When I was a medical student, DNA was thought to contain four bases--adenine, guanine, cytosine, and thymine--and to be comprised of a regularly recurring tetranucleotide structure--purine, pyrimidine; purine, pyrimidine. This putative structure for DNA had been taught as dogma for fifty years, since the days of P. A. Levine who proposed this structure in about 1900. Virtually every textbook of biochemistry of the first half of the twentieth century taught that structure.

In the early 1940s, DNA was established as genetic material, and questions were soon raised as to how DNA of such regular structure could contain genetic information. The development of chromatographic methods made it possible to analyze base ratios of purified, hydrolized DNA. This work was done principally by Edwin Chargaff of Columbia who found that the ratios of the four purine and pyrimidine bases were not always one to one to one to one. From extensive analyses of DNA from many species, he described certain regular relationships, later called by others "Chargaff Rules." These are as follows: (a) the sum of the purines (adenine and guanine) equals that of the pyrimidines (cytosine and thymine); (b) the molar ratio of adenine to thymine equals 1; (c) the molar ratio of guanine to cytosine equals 1. And, as a

direct consequence of these relationships, (d) the number of 6-amino groups (adenine and cytosine) is the same as that of 6-keto groups (guanine and thymine).

Chargaff had discovered some extraordinary principles of complementarity, but there he stopped. He did not attempt to speculate from his data on the primary, secondary, or tertiary structure of DNA. Meanwhile, others were addressing these problems. Pauling and Corey proposed a triple-stranded model of DNA, based on x-ray diffraction diagrams which they misinterpreted. Watson and Crick were building models of DNA and were aware of Chargaff's findings. They eventually came to a two-stranded double helical model of DNA which incorporated the Chargaff rules of complementarity, and fit the x-ray diffraction diagrams of Pauling, as later shown by Rosalyn Franklin. In their original publication in Nature thirty years ago this month they offered a suggested structure of DNA, and a hypothesis as to how this structure would encode information, form a basis for replication, for mutation, and heredity.

I find the contrasting contributions of Chargaff and of Watson and Crick enormously instructive. One is careful, analytical, precise, and cautious; the other is imaginative, synthetic, speculative, and insightful.

Yet in Chargaff's autobiography, "Heraclitean Fire," he writes of himself as "imaginative rather than analytical." I would have described him just the other way, another example of the difficulty in seeing ourselves as others see us.

Creativity takes many forms. It carries with it the spirit of inquiry and the application of curiosity and imagination leading to novelty and discovery. Imagination is a kind of latent creativity. It is natural for young people to be imaginative, and if this imagination can be coupled with discipline, its energy can be a life-long strength. The philosopher Alfred North

Whitehead called it a tragedy that "those who are imaginative have but slight experience, and those who are experienced have feeble imagination." He then generalized to say that "fools act on imagination without knowledge: pedants act on knowledge without imagination." The trick is to retain imagination while gaining a fund of experience and knowledge.

It is not easy to describe the process of creativity. Sir William Osler had his simple explanation for creativity that led to progress in medicine. He said, "A master word is directly responsible for all advances in medicine over the past 25 centuries. The master word is '<u>work</u>'."

But in Sir Alexander Fleming's account of the discovery of penicillin, a drastically different quality of creativity is suggested; namely, the added ingredient of <u>chance</u>. He said, "There are thousands of different molds and there are thousands of different bacteria and that chance put that mold in the right spot at the right time is like winning the Irish Sweepstakes."

The great French scientist, Claude Bernard, echoed Fleming's comment about the accidental nature of creativity but added a most important dimension to the thought. Bernard said that "experimental ideas are very often born by chance as a result of fortuitous observations. Nothing is more common and it is really the simplest way to begin a piece of scientific work. We walk, so to speak, in the realm of science, and we pursue what happens to present itself accidentally to our eyes."

The same thought was economically expressed by Franklin P. Adams when he said, "I find that a great part of the information I had was acquired by looking up something and finding something else on the way." Perhaps it is useful to emphasize the fact that the Adams' process was begun by looking up something. Serendipity is a dividend of activity. The word serendipity has an interesting history. It was invented by Horace Walpole in a letter he wrote

to a friend about a fairy tale, "The Three Princes of Serendip." Serendip was an ancient name for Ceylon or Sri Lanka. He wrote, "As their highnesses traveled they were always making discoveries, by accident or sagacity, of things which they were not in quest of." Serendipity has come to mean the discovery of one thing when in search of another.

In his recent book, "The Youngest Science," Lewis Thomas placed these insights of Claude Bernard and Franklin P. Adams squarely in the context of the physician researcher. He was discussing medical education and biomedical research of the 1950s and said, "The M.D. program was not then and still is not very satisfactory training for research in biomedical science. Then, as now, the Ph.D. program provided a much more rigorous and profound experience in science with a better grounding in the basic fields of biology needed for medical research. Earning an M.D. has, however, one enormous advantage that makes up in part for its deficiencies. After four years of medical school, it is impossible to think about a problem in biology or to read a paper without having part of one's mind trying at the same time to make connections with human disease."

I can't resist quoting further from Dr. Thomas' new book. In one of the paragraphs he expresses in his own colorful way what he considers to be a central truth about research. He said, "Making guesses at what might lie ahead when the new facts have arrived is the workaday business of science. But it is never the precise sure-footed enterprise that it sometimes claims credit for being. It has the sound of an intellectually flawless acrobatic act. The mind stands still for a moment, leaps out into mid air at precisely the millisecond when a trapeze from the other side is hanging at the extremity of its arc, zips down, out, and up again, lets go and flies into a triple somersault; then catches a second trapeze, timed for that moment, and floats

to a platform amid deafening applause. There is no margin for error. Success depends not so much on the eye or the grasp, certainly not on the imagination; only on the predictable certainty of the release of the bars to be caught--clockwork.

"It doesn't actually work out this way, and if scientists thought it did, nothing would get done. There would only be a mound of bone-shattered scholars being carried off on stretchers.

"In real life, research is dependent on the human capacity for making predictions that are wrong, and on the even more human gift for bouncing back to try again. This is the way the work goes. The predictions, especially the really important ones that turn out from time to time to be correct, are pure guesses. Error is the mode."

Last fall, while participating in the centennial observances of the University of Colorado Health Sciences Center, I met Dr. James H. Austin, Professor and Head of the Department of Neurology there. Dr. Austin has written extensively on creativity, and he gave me a copy of his recent book on the subject titled "Chase, Chance and Creativity--The Lucky Art of Novelty."

In Austin's examination of serendipity, he identifies four distinct forms of chance--accidental good luck, energetic motor activities in the right territory, a special kind of receptivity and discernment unique to the recipient, and a probing action with a distinctive personal flavor which courts Dame Fortune.

His book is filled with accounts of his personal experiences as a clinician and a scientist, and he draws from these experiences a demonstration of the role of creativity in teaching, research, and practice.

Any discussion of chance and creativity in science is incomplete without the moderating words of Louis Pasteur, "Chance favors only the prepared mind."

Throughout these characterizations of creativity, there are the contradictory concepts that would spell disaster for a marksman. They seem to be saying that you should aim carefully but not expect to hit the target in your sights. It brings to mind the advice given to night flyers during World War II who were told that dimly lit objects could only be seen if you did not look directly at them.

Creation in science is usually approached indirectly. There are often long periods when the person who is about to make an original observation appears to do nothing but take in information, work rather fruitlessly at seemingly trivial aspects of the problem, or give attention to unrelated matters. This is sometimes described as a period of "incubation." Following such a phase, the solution of a difficult problem or the occurrence of an original idea will often come all of a sudden in a leap of insight. It usually results from a dramatic change in the way the problem is perceived. Such a transformation can change a complicated problem into a simple one, and this sequence can be as descriptive of a difficult diagnosis as of a stubborn research problem.

It has been said that the two great enemies of creativity are mental rigidity on the one hand and wishful thinking on the other. These are evident when a person acts either in a far more regular way than the situation demands or else is incapable of perceiving the external realities that make his ideas infeasible. I would add a third, namely, imitation.

These barriers to creativity are of the most difficult kind because they are self-imposed. We tend to give undue importance to established patterns of thought and lock ourselves into conformity with them. We fear to challenge the obvious lest we appear naive. For some, this fear may be an insurmountable barrier. Jacques Barzun once remarked that one cannot learn to ice skate

or speak French without looking foolish, and that's why these skills are easy to the young who do not worry so much about appearances.

If you will permit one more personal digression, I would like to describe for you two contrasting behavioral patterns of two enormously creative scientists, Francois Jacob and Jacques Monod, of the Pasteur Institut in Paris, who shared the Nobel Prize for their discovery of messenger RNA. I was privileged to spend a year in that environment in 1963-64, and to participate in their Monday evening seminars for about ten months. Monod at that time was trying to understand enzyme regulation at the molecular level. There were two major theories. One called the induced-fit hypothesis championed especially by Daniel Koshland in which he envisioned a gradual and progressive accommodation of the macromolecule to its substrate or inhibitor as a result of contact between the protein and the ligand. The Paris school proposed the allosteric model, in which an enzyme might exist in two states, which Monod called the R&T states, for relaxed and taut configurations. He suggested that the substrate might bind with one form, an inhibitor with another, and when bound essentially remove the complex from an equilibrium state, thus progressively shifting the mixture toward either the R or the T state. Monod presented model after model of his allosteric ideas on successive Monday evenings, replete with diagrams and equations on the board. He was inviting the most searching and critical comment from the audience which consisted of many accomplished physical biochemists, and some of the criticisms were severe indeed. The colloquia were animated, vigorous, and searching, but totally devoid of any acrimony or ceremony. The youngest person in the group was free to destroy the teacher's model and Monod, always flamboyant, and highly articulate, enjoyed the sessions as his ideas were honed and improved. By contrast Francois Jacob, equally brilliant, equally creative, was quiet,

attentive, introspective. Perhaps in one seminar in four, that is, once a month, he would ask a short question for verification. These two great scientists, perfectly mated, worked together extraordinarily productively for 30 years with personalities that could not have been more different, yet in my view they were equally creative.

In an article in The Scientific American which appeared nearly 30 years ago, Morris Kline said, "The creative act owes little to logic or reason. In their accounts of the circumstances under which big ideas occurred to them, mathematicians have often mentioned that the inspiration had no relation to the work they happened to be doing. Sometimes it came while they were traveling, shaving, or thinking about other matters. The creative process cannot be summoned at will or even cajoled by sacrificial offering. Indeed it seems to occur most readily when the mind is relaxed and the imagination roaming freely."

Sudden hunches, hunches that lead to short, elegant solutions of problems, are called by psychologists "Aha! Reactions"--they seem suddenly to come out of the blue.

In his delightful little book called "Aha! Insight"--Martin Gardner examines the question, "Exactly what goes on in a creative person's mind when he or she has a valuable hunch? The truth is that nobody knows. It is some kind of mysterious process that no one has so far been able to teach or to store in a computer . . . the sudden hunch, the creative leap of the mind that sees in a flash how to solve a problem in a simple way, is something quite different from general intelligence. Recent studies show that persons who possess a high Aha! ability are all intelligent to a moderate level but beyond that level, there seems to be no correlation between high intelligence and this kind of thinking. Einstein, for instance, was not particularly skillful

in traditional mathematics and his records in school and college were mediocre. Yet the insights that produced his general theory of relativity were so profound that they completely revolutionized physics." Martin Gardner added one other idea which I think is worth considering. He said that psychologists are not sure, but studies of creative thinking suggest some sort of relationship between creative ability and humor, which has been defined as the sensation of sudden, unexpected pleasure. Perhaps there is a connection between hunches and delight in play.

It has been known for some time that brainstorming is an efficient technique for tapping the creative ideas of a group. It works best when the members of the group can suspend judgment, saving critical evaluation of ideas for later; when ideas are presented without inhibition, whether they are good or bad, sensible or silly; when there is a substantial number of ideas presented; and when there is cross-fertilization, examination of each of the ideas from the different perspectives of the individuals in the group.

According to Herodotus, the ancient Persians at the time of Cyrus the Great made a general practice of deliberating upon affairs of weight when they were drunk, and then on the next day to consider the matter again when they were sober. If they still approved of their drunken decision, they then acted upon it. Herodotus added, "Sometimes, however, they are sober at the first deliberation, but in this case, they always reconsider the matter under the influence of wine." I would interpret the laughter from the audience to indicate that you agree that this is, indeed, a means for removing barriers to creativity.

Brainstorming pertains to group consideration. It has valid counterparts, however, in the process by which an individual generates creative questions and answers.

Equating creativity to chance, to leaps of insight, to suspended judgment, to acceptance of ideas without evaluation is to trivialize the accomplishments of the men and women who have brought us to this exciting day in science. Once again, let me remind you of Pasteur's admonition that chance favors only the prepared mind.

Furthermore, I cannot overlook an obvious fact about this assembly. Most of you are medical students, training for a career in service to the suffering. Your service can take a variety of forms. In recent years, we have seen the powerful benefits of increased knowledge.

In an essay on the science and technology of medicine, Lewis Thomas addressed the question of medical care in global terms. "If," he said, "our society wishes to be rid of the diseases, fatal and nonfatal, that plague us the most, there is really little prospect of doing so by mounting a still larger health care system at still greater cost for delivering essentially today's kind of technology on a larger scale. We will not do so by carrying out broader programs of surveillance and screening. The truth is that we do not yet know enough."

Thomas went on to say, "But there is also another truth of great importance: We are learning fast. The harvest of new information from the biological revolution of the past quarter century is just now coming in, and we can probably begin now to figure out the mechanisms of major diseases which were blank mysteries a few years back as accurately and profitably as was done for the infectious diseases earlier in this century. This can be said with considerable confidence and without risk of over promising or raising false hopes provided we do not set time schedules or offer dates of delivery. Sooner or later it will go this way, since clearly it <u>can</u> go this way. It is

simply a question at this stage of events of how much we wish to invest for the health care system of the future in science."

Such public investment in science comes down to a highly personal and individual activity. As Alan Gregg has said, "Medical research is an abstraction. The realities are not the laboratories and the hospitals but the men and women who search again and again for causes."

More than a hundred years ago, Oliver Wendell Holmes commented to a graduating class that "Science is a great traveler and wears out shoes pretty fast, as might be expected."

Since that day, the pace of science and consequently of the practice of medicine has accelerated to a fantastic rate. Perhaps it is significant to note that many statues of the Roman god Mercury had him not only carrying a caduceus but also wearing winged sandals. It may be revisionist mythology, but it seems to me that a modern medical scientist might fairly be represented by the figure of Mercury carrying the aesculapian staff of healing, and wearing winged sandals to depict the creative leaps of original discovery.

Statement

By

James B. Wyngaarden, M.D.
Director
National Institutes of Health

Before the

Senate Committee on Labor and
Human Resources

April 25, 1983

I am pleased to address the high blood pressure control prevention initiative and report to you on progress in reaching the objectives set forth in the Public Health Service report: Promoting Health - Preventing Disease: Objectives for the Nation.

Controlling high blood pressure in the United States achieved priority status at the National Institutes of Health in 1972 when the National Heart, Lung, and Blood Institute (NHLBI) was given lead agency responsibility to develop and implement a national program. That effort today involves a number of Federal agencies including the Centers for Disease Control, the Food and Drug Administration, the Health Resources and Services Administration, and the Veterans Administration. But it is far more than a Federal program. Indeed, the strength and success of the program rests largely in the partnership that has been developed with the private sector as well as with government agencies at the State and local levels. For example, there are thirty member organizations currently on the Coordinating Committee of the National High Blood Pressure Education Program, which is administered by NHLBI. These include such professional organizations as the American Medical Association, the National Medical Association, and the American Academy of Family Physicians and such voluntary agencies as the American Heart Association, the National Kidney Foundation, and the American Red Cross. In addition, several large businesses and unions are working in concert with this program. That the effort extends through the States into the community is illustrated by the facts that every State Health Department participates in the Program and that there are approximately 2000 community-based high blood pressure control programs.

It is important to be conscious of the contributions made by the participants in the National Program, for it is only through their involvement that we will be able to reach the prevention objectives related to high blood pressure control.

Those objectives established for 1990 include: to achieve long-term control for at least 60 percent of known hypertensives in the United States; to reduce the average sodium ingestion to somewhere between 6 and 12 grams per day; to reduce the proportion of overweight men to 10 percent of the male population and of overweight women to 17 percent of the female population; to increase to 50 percent the number of adults who are able to identify the principal risk factors for coronary heart disease; to raise to 90 percent the number of adults who can state whether or not their blood pressures are in the normal range; to expand to 50 percent the number of processed food items labeled to inform the consumer of sodium and calorie content; to establish a system to determine the incidence of hypertension; and to develop methodology to measure the number of hypertensives who are aware or unaware of their condition, under care and not controlled, and under care and controlled.

All of these objectives are being addressed. In some cases, progress can be measured on the basis of periodic reports now in place, such as those stemming from the Health and Nutrition Examination Survey (HANES) and Lou Harris public opinion polls. In other cases, the data will be more difficult to obtain. Let me share with you some of the indicators we now have.

Just last September, the second Health and Nutrition Examination Survey (HANES II) reported on progress in the area of high blood pressure control. Included in the information from that survey was the fact that in the early 1970s, 49.1 percent of those with high blood pressure did not know they had it; by 1980 this proportion had dropped to 26.6 percent. Also in the early 1970s, only 16.5 percent of hypertensives who were on medication had their high blood pressure under control; by 1980 this had increased to 34.1 percent. Comparison of public opinion polls conducted by Lou Harris in 1973 and 1979 also provides indicators of progress. For example, in 1973, 38 percent of those surveyed knew that "normal" blood pressure was less than 140/90 mm Hg; by 1979, this number had increased to 63 percent. As to weight reduction and sodium restriction: in 1979, 67 percent of those surveyed realized that weight reduction could help lower blood pressure; 72 percent were aware of low-salt diets as a form of treatment. Also in 1979, 83 percent of those surveyed reported having their blood pressure checked within the past 12 months.

Perhaps the most impressive data can be found on cardiovascular mortality charts. High blood pressure is a major factor in coronary heart disease mortality and is the principal factor in stroke mortality. During the life of the national high blood pressure control effort, 1972-1982, we have seen an age-adjusted mortality decline for coronary heart disease of 25 percent and a mortality decline for stroke of 42 percent. I doubt if anyone would claim a direct cause and effect relationship. However, many learned observers would readily agree that progress in high blood pressure control has played an important part in this mortality decline.

These statistics are illustrative of the progress that has been made during the past decade, but they shed little light on how that progress was made. As I indicated earlier, the national high blood pressure control program involves many partners. I would like to give you a few examples of how this partnership works.

In 1979, the National Heart, Lung, and Blood Institute reported the findings of a major clinical trial, the Hypertension Detection and Follow-up Program (HDFP). This study found that vigorous, systematic treatment of even mild high blood pressure can be very beneficial; there was 20 percent less mortality among mild hypertensives in the HDFP study group. There was a general agreement in the scientific community that the HDFP findings warranted some updated guidelines for the health care system. A group of scientists and clinicians was appointed to a Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. This was the second such group formed and, after a year of deliberation, they produced a report to serve as a guide for those treating hypertensive patients. Most of the medical and public health organizations belonging to the National High Blood Pressure Education Program distributed this report to their memberships. Some carried it in full or in part in their respective journals. For example, the Annals of Internal Medicine, Chest, Hypertension, The American Journal of Cardiology, The Mayo Clinic Proceedings, The American Journal of Hospital Pharmacy, Public Health Reports, and The Journal of Practical Nursing all carried the report or portions of the report to their readerships. The report has received wide-spread usage and has helped health professionals in this country and in other

countries treat high blood pressure more effectively. I have brought a copy of the Joint National Committee Report to share with you, Mr. Chairman, and I understand that copies of the Report have been distributed to all of the members of the Committee.

Last September, we reported the findings of another major clinical trial--the Multiple Risk Factor Intervention Trial, known as MRFIT or Mr. Fit. While this trial also underscored the benefit of treating high blood pressure, it raised questions about when and how to treat mild hypertensives, particularly those with ECG abnormalities. Last week, at the National Conference on High Blood Pressure, held in Washington, the Director of the National Heart, Lung, and Blood Institute announced that he was appointing a new Joint Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. This Committee will analyze the MRFIT findings as well as data from other studies. They will also take testimony from physicians and scientists in the field. In a year's time or so, this Committee, too, will prepare a report which will serve as a guide to those who treat hypertensives. This will continue the cycle of acquiring new knowledge, testing it, analyzing the findings, and translating them for the practicing medical community and the public.

Medical associations have been very helpful in transferring program knowledge to their own constituents in order continually to improve the quality of high blood pressure control. There are other organizations associated with the national program which have been equally as helpful in educating the public. Organizations such as the American Heart Association, the National Kidney Foundation, the American Red Cross, and the Citizens for the Treatment of High

Blood Pressure have been very active in bringing educational messages directly to the public. Each has prepared patient education material for use within the health care system, as well as other messages and material for use within the mass media. The public education thrust is a crucial element in getting and keeping hypertension under control.

Within the past few years, there has been another partner which has become increasingly active. That partner is private business. More and more companies are establishing high blood pressure programs for their employees. Let me give you some examples. Staff members from NHLBI visited with the medical leadership at General Motors on the issue of high blood pressure control. As a direct result of that meeting, a program for employees was launched that is now serving nearly 750,000 employees of General Motors. There has also been long-standing mutual collaboration with firms such as Campbell Soup, Kimberly-Clark, and Johnson and Johnson in establishing high blood pressure control and cardiovascular risk factor reduction programs for employees. Many of these companies have taken a leadership role among their peers in advocating the establishment of worksite programs.

The program staff of the National Heart, Lung, and Blood Institute has also provided technical assistance to insurance companies such as Travellers and Metropolitan Life, which are promoting blood pressure control programs among their subscribers. Blue Cross/Blue Shield, with support from NHLBI, conducted pilot studies in Michigan and Connecticut to see whether agents of the insurance company could help convince subscriber companies to develop worksite programs. The programs were successful and data from the studies supported the hypothesis

that the worksite was an even more effective setting than the community in getting individuals to stay on their treatment. That hypothesis was also upheld in NHLBI-supported studies at the Ford Motor Company, Westinghouse, and in the State of Maryland.

This October, NHLBI is co-sponsoring, with General Motors and Metropolitan Life, a one-day conference for chief executive officers of major companies. The purpose of this conference is to present the latest data on the value of worksite programs as a means of stimulating new programs or improving existing ones. A number of companies have contributed to the national high blood pressure control effort by reprinting thousands--in some cases millions--of brochures and other educational materials for distribution to the public. The National Heart, Lung, and Blood Institute keeps a catalog which summarizes ongoing collaboration with a wide range of businesses and voluntary agencies in the private sector. I have attached a copy of that inventory to the testimony, Mr. Chairman, since I think you will find it of interest. I hope that it can be included as part of the Record.

There is little doubt that the many associations, groups, and companies actively working in this high blood pressure partnership have been largely responsible for much of its success. Another important factor contributing to the success of the effort is its research base. The program was launched in the early 1970s after the VA Cooperative Trials on hypertension demonstrated that there was life-saving value to the treatment of moderate and severe high blood pressure. The results from research have guided the program ever since.

There has been considerable research directed at obtaining a better understanding of the pathogenesis of hypertension. Some of the research of the past has contributed greatly to the pharmacological advances of the past decade. Much of the research now going on is seeking answers which will improve upon the effectiveness of current pharmacological agents while reducing the adverse or side effects of anti-hypertensive medication. We are also currently addressing a number of non-pharmacological research questions which relate directly to the Objectives for the Nation. We are engaged in a number of clinical research studies to determine the mechanisms of obesity-related hypertension and in investigations aimed at determining the role of dietary factors, including sodium, calcium, and potassium. While efforts to keep the public informed about sodium content, such as that being carried out by many food manufacturers in cooperation with the Food and Drug Administration, are important, it is equally important to understand better how sodium restriction contributes to high blood pressure control and to determine easily for whom this mode of therapy is beneficial. Research efforts also include examination of biofeedback, relaxation response, counseling, and other behavior-related methods for reducing blood pressure. Behavioral studies are also underway to examine better methods of encouraging adherence to therapy.

Surveys are often used to measure progress and to identify areas of need. As indicated in the Objectives for the Nation, there is a strong need to acquire incidence data related to hypertensive diseases. By having more accurate incidence data, we will be in a better position to understand the impact of blood pressure control measures. This past year, NHLBI began a pilot project

to document trends in mortality and morbidity from cardiovascular diseases. If the pilot phase proves successful, a program will be initiated fully in 1984 or 1985.

Another area of investigation supported by NHLBI is the study of how high blood pressure programs can be organized and implemented most effectively. Seven states are working with the NHLBI to test the hypothesis that blood pressure efforts can be more effective if state and local organizations have common goals and share resources and responsibilities. At the community level, 14 long-term high blood pressure control programs are being supported by NHLBI to determine how all relevant resources can be put to most effective use in urban or rural areas with poor or minority populations. Some of these programs are being carried out by the NHLBI in collaboration with the Health Resources and Services Administration.

Despite the considerable progress of the past decade, the problem of hypertension in the United States is a major one. It is the major factor contributing to the 500,000 strokes that occur each year and it is believed to be a significant factor in the million or more heart attacks that occur annually. The economic cost to the nation is estimated to be at least $8 billion per year. We will need to continue our efforts to marshall our resources effectively to make the best use of all the many organizations and agencies that make up the far-reaching high blood pressure network. At the same time, we will continue to seek answers to those questions so important to implementing effective control measures.

Research on pharmacological and non-pharmacological approaches to high blood pressure control will continue to provide the basis from which education and intervention efforts will spring. At the same time, research into the basic causes of hypertension will also continue unabated. This will be done through our primary research mechanism, the investigator-initiated project grant. Most of the $93 million we intend to spend in hypertension research in fiscal year 1984 will be in this area. For no matter how successful our control efforts become, our ultimate goal in addressing high blood pressure is to establish the cause or causes of hypertension and to prevent the disease altogether.

As you are aware, Mr. Chairman, May is High Blood Pressure Month. It is a time when all of us interested in high blood pressure control accelerate our efforts to keep the intensity and the growth in this national campaign. Among the activities initiated to assist in this objective is the High Blood Pressure Month Kit that we send to those in the field. I would like you to have one of these kits so you can see one of the tools we use in this national effort. I also understand that these kits have been provided to all the members of the Committee.

The challenge we face, is a major one when one considers that there are 60 million Americans with elevated blood pressure and that the incidence of heart attacks, stroke, and kidney disease related to high blood pressure remains high. We can take pride in the achievements to date, but we must be energetic in responding to the challenges of the future.

Private and Public Sector Collaboration
Office of Prevention, Education, and Control
National Heart, Lung, and Blood Institute, NIH

- January 1983 -

PRIVATE SECTOR - BUSINESS

Organization	NHLBI Activity	Results
# P&C Food Markets Headquarters (HQ) Syracuse, NY	Consulted on the implementation of the "Foods for Health"(FFH) program. Provided technical assistance in use and re-printing of the Eaters' Almanacs (EA). FFH was originally developed as a point-of-purchase nutrition education program with Giant Food. (see p. 5) Eaters' Almanacs (EA) is a 26-issue, bi-weekly handout which provides consumer information on cholesterol, calories, sodium, fats, and other heart health topics, also practical tips for changing buying and eating habits.	P&C printed and distributed 1 1/2 million copies of the Eaters' Almanacs in 150 stores. P&C conducted blood pressure screenings in store, mailed copies of EA to 200 nutrition educators in NY, MA, VT, NH, & PA on a bi-weekly basis, made 25 presentations of FFH materials. P&C is doing a nutritional analysis of EA recipes, and will distribute recipe cards with this information every two weeks thru Jan. '84.
# AT&T	NHLBI is surveying impact of Federal anti-smoking policies on various gov't agencies. Pacific Telephone is considering replicating the survey of anti-smoking policy effects at a number of Pacific Telephone workplaces.	NHLBI and Pacific Telephone will have comparable data to assess the effectiveness of anti-smoking policies in a variety of public and private sector workplace environments.
	Consulted on use and reprinting of Exercise and Your Heart† (E&YH) for AT&T Long Lines Co. in VA.	AT&T Long Lines reprinted 4500 copies for employees as part of their health program.
# Pfizer Laboratories, HQ New York, NY	Assisted in developing and producing a 5 pamphlet patient-education kit, Living with High Blood Pressure.	Provided 156,000 kits for NHLBI distribution.

= NEW ACTIVITY AREA

† - Exercise and Your Heart - An NHLBI publication about the relationship between exercise & your heart with practical guidelines for beginning and maintaining an individual exercise program.

Organization	NHLBI Activity	Results
# Coca-Cola, HQ Atlanta, GA	Provided technical consultation and reviewed materials for employee HBP* program.	Have ongoing high blood pressure control program for headquarters.
# Exxon Chemical Americas, Houston, TX	Consulted on use and reproduction of Eaters' Almanac (EA) as part of their cafeteria nutrition education program.	Exxon is distributing 750 copies bi-weekly; items in cafeteria are keyed to each EA issue. Other Exxon corporation headquarters are planning similar EA projects.
# Searle Pharmaceuticals Headquarters Skokie, IL	At NHLBI request, Searle is printing one million copies of the NHLBI publication, High Blood Pressure Facts and Fiction for use in May '83 High Blood Pressure Month, as they did for May '82.	Searle printed and delivered one million copies of Facts and Fiction to NHLBI for May '82 HBP* Month.
# Meredith Publishing HQ Des Moines, IA	Consulted on use and reprinting of Eaters' Almanac for employees.	Will print and mail all 26 issues of EA to 5000 employees bi-weekly.
# Russell Industries Bridgeville, PA	Consulted on the use and duplication of EA for paving company employees.	Reproducing 200 copies of issues as a payroll stuffer.
# Sentinel Star Newspaper Orlando, FL	Consulted on the use and reprinting of EA and Exercise and Your Heart (E&YH) for employee health program.	Reprinted 1200 of E&YH, will begin printing EA in '83.
# Olsens Market Place Stores, Yuma, AZ.	Consulted on use and reprinting of EA as part of in-store nutrition education program.	Reprinting and distributing EA 1500 of all 26 issues, mailing to some customers. 40,000 in total.

= NEW ACTIVITY AREA

* - HBP - High blood pressure, also known as hypertension.

Organization	NHLBI Activity	Results
General Motors Headquarters, Detroit, MI	Consultation and on-site visits to assist GM in developing their high blood pressure (HBP) control program.	As a result of NHLBI involvement, GM has instituted HBP control program for nearly 750,000 employees world-wide.
	Two epidemiology seminars developed by NHLBI and AOMA* presented to GM physicians.	Physicians are applying data collection and evaluation principles at the workplace.
	# NHLBI collaborating with GM and Metropolitan Life to present data-based conference for business decision-makers about workplace CVD*** risk factor reduction.	Conference to be held in 1983. (See following Metropolitan Life item.)
Metropolitan Life Headquarters, New York, NY	# Met Life collaborating in conference with GM and NHLBI in item above.	
	Reviewed the development and design of MET-50, a study of health promotion programs for small business.	Met Life is beginning to implement MET-50 program.
	Provided preliminary data of success rates in MRFIT** smoking cessation programs.	Met Life considered data in their own smoking cessation programs.
	Consulted on the health education component of the Center for Health Help, a health promotion program for the New York office.	The Center for Health Help is now being marketed to clients across the U.S.
	Provided CVD*** risk factor baseline data for evaluating the Center for Health Help.	Met Life is proceeding with their evaluation using the baseline data.

\# = NEW ACTIVITY AREA

* AOMA - American Occupational Medicine Association - see p. 7

** MRFIT- Multiple Risk Factor Intervention Trial, a clinical study to determine the efficacy of controlling hypertension, reducing elevated blood cholesterol, and stopping smoking to prevent the incidence of heart attack.

*** CVD - Cardiovascular disease, disease of the heart and circulatory system.

Organization	NHLBI Activity	Results
# Provident Life Insurance, HQ Chattanooga, TN	Consulted on use and reprinting of Eaters' Almanac (EA) as part of adopting "Foods for Health".	Will reprint 10,000 copies of EA for employees and clientele.
Travelers Insurance, HQ Hartford, CT	Assisted in the development and design of a high blood pressure (HBP) program for group subscribers in Florida and New Jersey.	This program may be offered nationwide to Travelers' group subscribers. Adopted in Florida.
National Life Insurance, HQ Nashville, TN	NHLBI requested that National Life (N.L.) print one million HBP Pressure Facts and Fiction, an NHLBI publication. A large percentage of N.L.'s clients are Black.	Publication distributed with N.L. logo to clients and general public. Also, National Life printed 75,000 Spanish HBP Facts and Fiction.
Blue Cross/ Blue Shield Headquarters Chicago, IL	Under NHLBI contract, BC/BS developed a program to train Michigan and Conn. account executives to market HBP control programs to industry group subscribers.	Many businesses in Michigan and Connecticut established HBP programs. So far, this success has convinced 29 of the 103 BC/BS plans and other insurance companies to follow suit in marketing HBP programs.
	Assisted BC/BS in developing health promotion materials on HBP, smoking, and nutrition.	BC/BS is developing a cardiovascular disease (CVD) risk reduction program for the worksite.
	Assisted in the research design of the Michigan BC/BS worksite CVD risk reduction area	The study successfully reduced workdays lost and morbidity due to CVD.
Hoechst Fibers HQ Greenville, SC	Evaluated company HBP control program in cooperation with state and local agencies.	Program is operational

= NEW ACTIVITY AREA

Organization	NHLBI Activity	Results
Giant Food Headquarters Washington, DC	Jointly developed and carried out Foods for Health, a pilot nutrition education program using the point of food purchase - 90 stores in the Washington area - as the educational setting. The primary consumer education vehicles were the Eaters' Almanacs and a variety of posters and signs.	Program demonstrated the feasibility of working with supermarkets in nutrition education. Evaluation indicated increased program awareness and nutrition knowledge by Giant shoppers. Several other food chains and other organizations have adapted Foods for Health as part of their own education programs. (See pp. 1,2,4,6, 12,13)
Boeing Aircraft HQ Seattle, WA	Consultation and on-site visit to discuss value of high blood pressure (HBP) program.	Active program; now includes other CVD risk factors.
Ingersoll-Rand HQ Painted Post, NY	Consultation and collaboration with ongoing HBP control program.	Program active with strong community component.
Campbell Soup HQ Camden, NJ	Longstanding mutual collaboration and consultation in health promotion and disease prevention activities.	Active program, now serves as resource to other companies and agencies.
Kimberly-Clark HQ Stevens Point, WI	Longstanding mutual collaboration and consultation in health promotion and disease prevention activities.	Model comprehensive program, serves as consultant to others.
Boehringer-Ingleheim HQ Ridgefield, CT	At NHLBI suggestion, they are preparing a comprehensive education program on the treatment of hypertension for medical school educators.	Packages to be distributed at medical schools.

Organization	NHLBI Activity	Results
Johnson and Johnson Headquarters New Brunswick, NJ	Longstanding collaboration in worksite health promotion and disease prevention activities.	Improved ongoing epidemiologic study on cardiovascular disease (CVD) risk factor reduction; J&J may provide cost data.
	Consulted on use and reprinting of Eaters' Almanac (EA) and related recipes.	Using selected EA issues in employee nutrition classes.
Burlington Industries, HQ Greensboro, NC	Collaboration in high blood pressure (HBP) workplace control program.	Program active; serves as consultant to others.
General Electric HQ Stamford, CT	Made presentation at '81 GE Health and Safety Conference on CVD health care costs, using GE's own data.	Improved GE plans for CVD control efforts.
Ford Motor Company, World HQ, Dearborn, MI	Longstanding collaboration in assisting worksite health promotion activities.	Strengthened CVD risk reduction program.
Vita-Stat HQ St. Petersburg, FL	NHLBI assisted them in developing HBP worksite cost card calculator. (Vita Stat makes automated blood pressure measuring devices.)	Card is being distributed nationally. Continuing collaboration.
Merck, Sharp, and Dohme, HQ Rahway, NH	NHLBI requested their support in printing The Community Guide to HBP Control.	Approx. 8000 guides will be printed for NHLBI.
	NHLBI asked for their support in printing The Practicing Pharmacist's Handbook for HBP Control.	Guides distributed to pharmacists.
	NHLBI requested their assistance in producing the first airport posters for test showings in Washington and N.Y. airports.	Posters distributed nationally by Transportation Displays Inc. (see p. 11)
Upjohn, HQ Kalamazoo, MI	NHLBI asked their assistance in developing and distributing 2500 HBP posters for Hispanic populations.	Posters distributed nationally.

Organization	NHLBI Activity	Results
# Farmers' Insurance Mankato, MN	NHLBI and ALA requested their help in placing a full-page ad in newspaper for Quit-Smoking program. (see next item)	Ten agents funded an ad which an estimated 44% of Mankato smokers saw, informing them of the program.
VOLUNTARY AND BUSINESS ASSOCIATIONS		
# American Lung Association (ALA) Headquarters, New York, NY	NHLBI asked their cooperation in developing and distributing a smoking cessation TV module with a community focus.	NHLBI and ALA jointly developed TV-Community Quit Smoking Program based on the ALA quit kits and an NHLBI-produced TV quit-in-one-week module. NHLBI and ALA are marketing and evaluating the program in ten selected communities. ALA will then offer the program to their affiliates.
American Heart Association (AHA) Headquarters, Dallas, TX	Longstanding mutual collaboration in health promotion and disease prevention in industry.	Collaborated in development of AHA Worksite CVD Risk Factor Reduction Program Directory.
American Occupational Medical Assoc. Headquarters, Chicago, IL	Longstanding mutual collaboration in health promotion and disease prevention in industry.	Collaborative development of epidemiology seminars for occupational physicians. NHLBI arranged presentations at AOMA Health Conferences.
American Assoc. of Occupational Health Nurses Headquarters, Atlanta, GA	Longstanding mutual collaboration in CVD health promotion and disease prevention.	NHLBI presentations at last three AAOHN conferences.
	In consult with the NHLBI, the Nov.'81 AAOHN Journal was devoted to worksite HBP control.	Issue has been distributed.
American Farm Bureau Federation HQ Chicago, IL	NHLBI assisted in developing a HBP control initiative for the entire membership.	One year effort beginning July, 1982.

= NEW ACTIVITY AREA

Organization	NHLBI Activity	Results
Medical Directors of Life Insurance Companies	NHLBI jointly developed report "The Underwriting Significance of High Blood Pressure" with the Medical Directors.	Insurers considered the report to reduce premiums for controlled hypertensives.
	NHLBI provided consultation on the development of the report "The Underwriting Significance of Cigarette Smoking".	Data being analyzed. Marketing plan for report is being developed.
West Coast Consortium of Health Insurance Brokers	NHLBI made three presentations at workshops on the effectiveness of cardiovascular disease (CVD) risk reduction programs for the worksite.	Atlantic-Richfield and North American Phillips have accelerated development of their CVD risk reduction programs.
National Chambers of Commerce HQ Washington, DC	Ongoing relationship concerning health issues in the workplace.	Gave presentation on CVD risk reduction at '81 convention, Primer* distributed to business coalitions.
Association for the Advancement of Health Education and the Society of State Directors of Health, Physical Education, and Recreation Kent, OH	Technical assistance to identify the health information needs and current information sources of the State Directors, and to assess the potential for their network to distribute Exercise and Your Heart (E&YH) and future health information	AAHE & SSDHPER implemented a health information survey. The State Directors redistributed 67,000 copies of E&YH.
Association for the Advancement of Health Education Reston, VA	Assisted in the development of the Jan. '82 issue of Health Education (AAHE Journal) focused on "Cardiovascular Health & the School-Age Child."	National distribution of this issue, thousands of reprints ordered. American Heart Association has also reprinted and distributed the issue.

*Cardiovascular Primer for the Workplace - An NHLBI publication which provides both the why and the how-to for establishing a CVD risk reduction program for employees.

Organization	NHLBI Activity	Results
Salt Institute Alexandria, VA	Assisted in the development of pamphlet, *Straight Talk About Salt*.	*Straight Talk About Salt* printed and distributed.
Food Marketing Institute Washington, DC	Assisted in the development of pamphlet, *Sodium Sense*.	*Sodium Sense* printed and distributed.

In addition, the following associations published issues of their journals which were entirely devoted to HBP detection, treatment and control. The articles were planned and edited with the assistance of the NHLBI.

American Nurses Association	American Dental Association	American Rural Health Association	American Pharmaceutical Association

UNIONS		
# Int'l Rubber Workers Union Akron, OH	Provided information and consultation for article on high blood pressure (HBP) detection and control for their journal, *Safetylines*.	Article in Jan.83 issue of *Safetylines* which goes to 600+ locals and OSHA groups.
United Steel Workers of America (USWA) Pittsburgh, PA	Screened the membership at the '79 national conference, evaluated the data and presented results to Board of Directors	As a direct result of NHLBI involvement, USWA is conducting a HBP control program for its membership.
Amalgamated Clothing and Textile Workers New York, NY	Consultation for their HBP efforts as part of NY State Program.	Willing to promote HBP control to other unions and labor organizations.

= NEW ACTIVITY AREA

	Organization	NHLBI Activity	Results
	MEDIA LEVERAGING		
#	KEYC-TV Mankato, Minn.	NHLBI requested their assistance in producing a pilot version of the Quit-Smoking Program (see p. 7).	KEYC produced pilot TV newscasts which received a very favorable share of viewing audience survey.
#	WBAL-TV Baltimore, MD.	NHLBI requested that WBAL produce the Quit-Smoking Program.	WBAL produced it in October 1982, they are assessing results and impact.
	Good Housekeeping Magazine New York, NY	NHLBI provided technical assistance in the adaptation of Exercise and Your Heart (E&YH) for a special health section insert, "The Save-Your-Heart Exercise Book".	Condensed version appeared in January '82. Good Housekeeping has 5 million paid circulation, approx. 20 million readers.
	National Association of Broadcasters (NAB) Washington, DC	NHLBI asked their consultation on "The Silent Disease" module.	NAB reviewed the pilot module, and recommended expanding the initial distribution from 25 to 50 TV stations.
	WBAL-TV Baltimore WHSV-TV Harrisonburg,VA WBTV-Charlotte,NC KDKA-TV Pittsburgh,PA WXEX-TV Petersburg,VA	NHLBI requested their participation in testing the pilot module of "The Silent Disease".	These stations broadcast the pilot and made recommendations on improving the program, enchancing its feasibility and effectiveness. They also helped plan national distribution of the modules. That distribution has resulted in 61 commercial TV stations, 15 cable TV, and three state educational TV stations producing the module.

= NEW ACTIVITY AREA

* - "The Silent Disease" is a half-hour TV program module on high blood pressure. It is completely scripted for local stations to produce, using local experts. Slides and animation are included.

Media leveraging cont'd

Organization	NHLBI Activity	Results
US Air Magazine Washington, DC	NHLBI collaborated with U.S. Air developing a series of monthly columns on nutrition and heart disease for their in-flight magazine.	US Air carried 12 full-page monthly articles providing new and different message to 1.4 million readers.
Neighborhood Theaters Richmond Newspapers, Inc. Petersburg Newspapers, Inc. Petersburg, VA. "You and Your Health" Syndicated Column Medical College of VA VA Commonwealth University	NHLBI asked assistance in surveying the effects of high blood pressure (HBP) medial messages on health professionals in the Richmond, Virginia area.	The papers and theaters donated space to carry HBP blurbs, and the university provided facilities for a press conference with the NHLBI director. Health professionals were then surveyed to assess the effect of these events on their recall. This provided unique insight into the media habits of doctors, nurses, and other health professionals.
Transportation Displays, Inc. (TDI) New York, NY	NHLBI requested their help in reaching the important audience of three million mostly middle-aged mostly male airline passengers.	From '78 through '81 provided almost exclusive free advertising space for NHLBI heart-health messages, posted at 80 airports nationwide.
Ackerly Airport Advertising (acquired TDI in '81) New York, NY	NHLBI asked if they would continue to assist in this project.	Ackerly provides free diorama posting space in 25 airports, also advice on using this more dramatic display technique.
PUBLIC SECTOR		
# US Armed Forces Information Service	NHLBI provided consultation on the use of Exercise and Your Heart as a primary resource for developing 52 radio and TV spots on physical fitness. Also provided technical assistance and advised on adaptation.	Reaches potential audience of 1,000,000 including all overseas personnel and their families.

= NEW ACTIVITY AREA

Public Sector cont'd

	Organization	NHLBI Activity	Results
#	US Army	Consulted on the use and reprinting of the Eaters' Almanacs (EA) to reach Army audiences through Art and Features, a feature service provided to Army newspapers and magazines.	Reprinted the entire text of EA in an issue of Art & Features, being picked up and duplicated by papers and magazines with combined circulation 700,000.
		NHLBI adapted EA, in cooperation with the Army Surgeon General's office, for distribution to soldiers and their families. EA posters and shelf signs are also to be printed and distributed.	Army Surgeon Gen's. Office will reprint EA and send 26 issues to be distributed by the 171 Army commissaries worldwide. Circulation may be 8 to 13 million copies.
		Providing other health education materials and consult for the Army fitness program, may develop evaluative survey for EA program.	Evaluation in planning stages.
#	US Navy	Consulted on use and reprinting of Exercise and Your Heart (E&YH) in Navy Lifeline, the Navy's health and safety magazine.	Reprinted the entire text of E&YH as four installments in Navy Lifeline magazine, sent to 30,000 armed forces health & safety professionals.
		Consulted on use of E&YH as part of developing their newly launched "Fitness for Life" program.	Redistributed 500 copies to Command Fitness Coordinators within each Navy unit in Navy health promotion kit.
		Providing further health education materials and consultation particularly to nutrition aspects of the Navy program.	Program is developing, contact is ongoing.

= NEW ACTIVITY AREA

	Organization	NHLBI Activity	Results
#	Tennessee Valley Authority	Consulted and provided materials for planning agency-wide HBP program.	Plan to impement a high blood pressure (HBP) control for employees.
#	Georgia Dep't of Health and Human Resources.	Consult on use of Eaters' Almanac (EA) as the focus of a nutrition education project in GA. Also consulted on media promotion and designing the evaluation of the program.	Plan to reprint and distribute EA to two test counties, then move to statewide distribution based upon evaluation. May distribute in Atlanta immediately if voluntary agency commits '83 funds.
#	Maryland Dep't of Health	Consulted on use and reprinting of Exercise and Your Heart (E&YH) as part of health promotion project, Healthy People.	Reprinting 2000 copies with local identifiers on cover and end of book
	State of Connecticut	Consulted on the use and reprinting of E&YH for state Risk Reduction Program.	Reprinted E&YH for distribution statewide.
		Collaboration on CVD risk factor reduction programs in industry.	Test state for NHLBI Blue Cross/ Blue Shield Insurance Contract. (see p. 4).
	New York State	Ongoing collaboration and cooperative activities with state Dep't of Health on workplace education and resources.	Have active workplace health promotion campaign.
	Royal Canadian Mounted Police	Consulted on use and duplication of Dietary Management of Hyperlipoproteinemia (DMH).	Diet booklets now being given out by Mountie physicians in Mountie clinics.
	Universidad Nacional de La Plata, Argentina.	Consulted on the translation of DMH into Spanish, and its reprinting.	Spanish version of DMH now distributed to patients in hospitals affiliated with the university.

= NEW ACTIVITY AREA

THE POLITICS OF THE BUDGETARY PROCESS*

by

James B. Wyngaarden, M.D.**

First off, I will confess that I borrowed the title for this talk, "The Politics of the Budgetary Process," from the classic of that name written by Aaron Wildavsky in 1964. Since the book was written, a number of changes have taken place in the names of the Government agencies involved and sweeping alterations have been made in the congressional mechanisms for dealing with the Federal budget. But the roles of the principal players are about the same as they were. The book is well worth having and I highly recommend it to you.

It might be said that there is something masochistic about my selection of the budget as a topic for a speech at this particular time. For the past three weeks, the Directors of the various operating components of the National Institutes of Health and I have been involved in that major event of the annual budget cycle known as the appropriations hearings. At these command performances before both the House and the Senate Appropriations Committees, our role has been to "defend the President's budget."

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*Luncheon Address, presented at the Spring Meeting of the Association of Professors of Medicine, Sheraton Washington Hotel, Washington, D.C., April 29, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

My initiation into the mysteries of the Federal budgetary process has been a fascinating, if demanding, learning experience. Although as of the end of the day today I will have completed my first full year as Director of the NIH, I consider myself still to be serving a novitiate in the politics of the budget. It is from this perspective that I will make a few observations about the role of the Director in the development, defense, and execution of the budget of the National Institutes of Health.

Wildavsky addressed the budgetary process pragmatically. He remarked that the proposed budgets submitted by Federal agencies may represent their aspirations, and since the amounts requested often have an effect on the amounts received, they are often strategies. He sees in the repeated interchanges that occur during the development of a budget the development of a communications network, and, once adopted, a budget becomes a precedent. A budget is all of these things. It represents expectations and aspirations. It is a strategy; it generates intensive and sustained communications; and one year's budget becomes a precedent for the next. It usually is the basis for the development of the budget for the following year.

From another point of view, the budget process represents a sort of multidimensional chess game. At this moment the NIH Director's office must be concerned with budgets for three different fiscal years. We are just past mid-year in execution of the FY 1983 budget and we are in the process of defending the President's budget request for FY 1984. Meanwhile, the process of

formulation of the FY 1985 budget is well on its way. The fact that we are developing a 1985 budget at a time when we are very uncertain as to what the actual 1984 budget will be adds a certain air of adventure and excitement to the exercise.

I. F. Stone has revised McLuhan's familiar dictum to make it read, "In Government the budget is the message."

While the budgets of the components of the National Institutes of Health do not communicate the excitement of the substance of science, a careful reading of them yields strong evidence of the policy directions of the agency. For example, the long-standing commitment of the NIH to the investigator-initiated research grant as its principal mechanism for the support of biomedical research stands out quite clearly in the annual budget summaries over the past several years. Recently almost exactly 50 percent of our total annual budget has been dedicated to such investigator-initiated grants. However, the many and complex forces that also have a part in shaping the outcome of the budget in any particular year are less easily discerned from the document itself.

Wildavsky's description of the budget process as the establishment of a network of communication is indeed an apt one. Fiscal authorities speak of the process as an iterative one. Reiterative might be a better adjective. To illustrate my point, let me sketch briefly the development of the 1985 budget and project the landmarks ahead of us on the road to its approval. During the late fall and early winter of last year, I held a planning and appropriation briefing session with each of

the Bureaus, Institutes, and Divisions of the NIH. These sessions have turned out to be some of the most rewarding activities that I have engaged in since becoming Director. At the sessions I was given firsthand reports of exciting new developments and directions in research and shared with the program administrators in the planning for the coming year. These briefings provide an opportunity for the Bureau, Institute, and Division Directors to articulate their programs and to discuss opportunities, problems, and issues to be considered in the development of the NIH research plan.

In early May the various constituent units will be submitting their individual budget proposals for consolidation into an overall NIH plan. During the month we will pull it all together and submit a preliminary NIH budget to the Public Health Service for consideration by the Assistant Secretary for Health.

In June the schedule calls for submission of the preliminary budgets of all of the agencies of the Public Health Service and the other parts of the Department to the Secretary for Health and Human Services. At about that time, the Office of Management and Budget will make known to the Department its total preliminary allowance. During July and August the Secretary will evaluate the preliminary proposals of all the units of the Department and adjust them when necessary in an effort to bring them near to the dollar target given the Department by the OMB.

In September, the Department's draft budget will be submitted to the OMB and in November, probably about Thanksgiving time, the OMB's proposed allowance will be made known to the Department. In

the following two or three weeks, opportunity will be provided for the Secretary to appeal to OMB and possibly to the President for the restoration of funds that might have been cut in the OMB allocation. Sometime in late December the final decisions are scheduled to be made and the President's budget put together. It then will be submitted to the Congress, probably in the last week in January, and shortly after that the hearings will begin.

When the President submits his request for FY 1985, the proposals he transmits pertaining to the NIH will have been in development over a period of more than a year. In enumerating the landmarks leading to the development of the President's budget submission, I should emphasize that each step in its progression involves a great deal of discussion and sometimes argument, first within the NIH, later within the Public Health Service, later within the Department, and then, of course, finally with the OMB. It is during these periods that the program managers, including the Director of NIH, have the opportunity to influence the development of the President's budget.

For example, it was during the budget development period three years ago that the decision was made that the NIH should endeavor to "stabilize" its annual allowance for new and competing grants. To dampen the roller coaster fluctuations in the number of new grants from year to year, a policy decision was made to attempt to stabilize such grants at approximately 5,000 each year. This stabilization effort has continued to be a dominant factor in our budget development, certainly in the budget now before the Congress. If you have been following the 1984 NIH

budget closely, you will know that when President Reagan presented his requests in late January he asked for a total of $4.077 billion for the NIH. However, at the time our supporting documents were prepared to go with the President's budget, the NIH estimated that it would be able to make only 3,676 new and competing grants. When the budget was submitted, Secretary Schweiker addressed a letter to Congress stating that stabilization continues to be a Departmental policy and that NIH would propose to make 5,000 new and competing grants during 1984. He left open the possibility that additional funds might be required. Subsequently, just ten days before our hearings, the OMB reaffirmed the stabilization policy but directed that we rearrange our budget so that we could make 5,000 new and competing grants allowing no increase in the overall total of the original request. Something had to give.

At this time, I will not go into the details of our adjustments since the point of my relating this saga is to emphasize the powerful and lasting effect of a single policy decision--that is, to stabilize the awarding of new grants.

Thus the FY 1984 budget we have presented and defended before the Committees of Congress totals $4.077 billion.

I use the word "defend" advisedly, for one of the basic rules and traditions regarding the budgetary procedure is that once the President has made his decision and has presented his budget request to the Congress, it is our proper role as program heads to defend and not to attempt to subvert the process by special pleadings. So, we sometimes have the surprising spectacle of a

Department head, whose budget has been cut drastically, refusing to admit that his agency has been wounded and repeating to the Congress the rationale for the cuts, a rationale that he only a few months before had bitterly opposed in the inner councils. One can almost hear the voice of a latter day Job intoning the ancient words: "Though he slay me, yet will I trust him."

Lest it appear that I am lodging a complaint against the current Administration, let me read to you from a memorandum written by President Harry Truman in November 1946 on the subject of budget busting. President Truman, himself a former Senator, was probably more aware than most of what could happen in a hearing. His memorandum to the Director of the Bureau of the Budget said:

"The estimates which I transmit to Congress reflect a balanced program for the Executive Branch as a whole and each individual estimate is considered in the light of this program. While agency witnesses before congressional committees must feel free to supply facts in answer to questions of committee members, I cannot condone the practice of seizing upon any opportunity which presents itself to indicate an opinion either directly or indirectly that my estimates are insufficient."

Mr. Truman went on to say: "When you notify the heads of the various departments and the agencies of the amounts to be included in the 1948 budget for their activities, I wish you would include a reminder that I shall expect them and their subordinates to support only the President's estimates in hearings and discussions with Members of Congress."

These 1946 instructions have been reaffirmed by every President since. Members of the Appropriations Committees, of course, are well aware of the instructions under which we operate.

A basic bureaucratic principle is: "Thou shalt not commit the crime of 'budget busting.'"

Citizen witnesses are not bound by the discipline that applies to agency officials, and they are free to make appeals for increases of funding for any particular program in which they have interest. I am sure that a number of you have appeared from time to time as citizen witnesses, as have I, and that you have pounded the table in behalf of programs that you felt to be vitally important. As Director of NIH I am not allowed that privilege.

Even though the budget requests are fixed by the President, the appropriations hearings give us an opportunity to explain to the Members of Congress in some detail the rationale for the figures that appear in the budget request and to clarify misunderstandings that occasionally arise over terminology. At our recent Senate hearing, for example, we were questioned as to why over half of our research grants are awarded without competition. At first we were puzzled by the question and then realized that the Senator was referring to the classification of investigator-initiated grants called "noncompeting," which, of course, is the category of grants continuing into their second and third years and is the terminology we use to distinguish them from the new and competing grants.

Considering the complexity of a budget like ours, the hearings are quite brief. Perhaps by keeping them short we avoid

the difficulty reported by Herodotus when he told of a delegation that appeared before the Spartan Magistrates seeking a grant of food. In the historian's words, "They had audience of the Magistrates before whom they made a long speech as was natural with persons greatly in want of aid. Accordingly, at this first sitting the Spartans answered them that they had forgotten the first half of their speech, and could make nothing of the remainder."

In keeping with the Spartan approach, a great many of the questions from Committee members are not actually asked at the time of the hearing but are submitted in writing. We are now in the process of answering over 500 questions from members of the Senate Appropriations Committee for publication as part of the hearing record.

Wildavsky spoke of budget strategies, a subject not totally foreign to a medical school department chairman. I suppose this art form is highly developed in Washington because so many bright people ponder the problem throughout the year. One of the best known is the Washington Monument ploy, whose name originated with the probably apocryphal story that when the Department of the Interior was threatened with a reduction it decided to make up part of the loss by closing the Washington Monument to tourists, relying upon the outcry which would certainly be generated to force the Congress to restore the cut.

Historically, program officials have been accused of using the Washington Monument gambit when they offer up popular programs, knowing that an across-the-board, uniform cut on all

programs would essentially be invisible and would be greeted by many a dry eye in the Congress. But such shuffles are merely tactical exercises when compared with certain budget strategies that have had substantial influence on the NIH budget as well as its organization. I am speaking of movements to create new Institutes. Invariably originating outside the agency, these strategies are developed by advocates of increased funding for research on a particular health problem. They reason that the creation of a new categorical Institute will focus more public and congressional attention on the subject disease and that Federal support of related research will be increased. Admittedly, this strategy has been successful in a number of instances, and the names of most of the eleven Institutes bear witness to these successes. But there is also a reverse effect of such strategies resulting in a trend toward fragmentation of the fundamental science base on which all research must rest--and an inevitable increase in overhead cost. It is for the latter reasons that we have generally opposed recent proposals for the creation of new Institutes.

In the past few years ten new Institutes have been proposed, and legislation for the creation of an Institute of Arthritis and Musculoskeletal Diseases is now pending in the Congress. In spite of our concerns about these strategies, we are not opposed to carefully considered changes in the structure of NIH. We recently negotiated a contract with the Institute of Medicine, of the National Academy of Sciences, for a comprehensive evaluation of the organization of the agency. Accordingly, we believe it

premature to legislate extensive organizational changes before the IOM study is completed and its recommendations are reviewed.

The NIH has been fortunate over the years, probably because the Congress has had a strong sense of the importance of the mission of the NIH and generally a feeling of approval of the way in which it has carried out its mission. In the past, at least, the Congress had almost invariably approved a higher budget than was requested by the Administration. This was so well known that, in his book on the budgetary process, Wildavsky used the NIH as an example of the special problems faced by the Bureau of the Budget. Permit me to quote a paragraph. He starts off with a question, "How much should be devoted to medical research sponsored by the Federal Government?" He answers, "Most of us would say quite a lot, but how much is that . . . ?" No one really knows how much medical research might be carried on profitably in some sense and the BOB people have discovered that there seems to be no end to the work qualified people believe it is desirable to attempt."

Then Wildavsky says that the BOB asks a political question: "How much is our society willing to spend?" But in the case of the NIH, there is not yet agreement on a fair share. Nor is there another formula, however arbitrary, such as devoting one percent of the gross national product or allowing a rise of ten percent a year which justifies a course of action. So, the author observed: "The BOB has the choice of cutting NIH arbitrarily and being drastically overridden by Congress, or of raising it arbitrarily and feeling that the situation has gotten out of hand."

There are those who say that the budget making process is essentially a ceremonial dance, and regardless of how gracefully the steps are executed results will always be the same. I do not subscribe to this view but at the same time recognize that there are only a few points in the process at which the NIH Director can successfully intervene. His greatest influence is in the effectiveness of his leadership over the long term.

I believe that the final outcome of an agency's budget proposal in a given year is the result of many forces acting upon the Administration and the Congress. In the absence of national emergency or severe economic distress, the principal determinant of the budget of an organization like the NIH is rooted in the public's regard for the mission and its general perception of the performance of the agency.

THE FEDERAL GOVERNMENT'S ROLE IN BIOMEDICAL RESEARCH*

by

James B. Wyngaarden, M.D.**

Thank you very much Dr. Bulkley. This symposium is entitled "A Federal Science Policy." I have been asked to discuss the Administration's FY 1984 budget for NIH. I am tempted to quote from Irving Stone when he says, "In government the budget is the message." The 1984 budget conveys a rather strange message. Bear in mind that 1984 is the year George Orwell wrote about. I thought I might provide a brief background before dealing specifically with current issues--to set the stage more broadly.

A percentage of those in the audience, including myself, first became intimately involved with the NIH during the "Shannon years" from 1955 to 1968. When Jim Shannon became Director of the NIH, its budget was $82 million a year. When he left 13 years later it had passed $1 billion. It had increased twelvefold in constant dollars in the 13-year period. During that stretch money was readily available, but there was a relative shortage of scientific ideas and of trained investigators. Shannon and his associates set about to build the scientific capability of this country and they did that very well. The NIH budget began to level off in 1968. Since the early 1970s it has not increased very much in constant dollars.

The situation I described in the Shannon years has in a way reversed itself. Money has become very tight at a time when there are many superb

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**Director, National Institutes of Health, Bethesda, Maryland

scientific ideas and a cadre of excellently trained investigators eager to work on them. There is, in a sense, an element of waste of a very valuable national resource--the trained scientist--brought about by the constraints of the budget. (First slide please.) The first slide shows the budget trends of the last decade. The current dollar budget has increased from about $1.5 billion in 1972 to over $4 billion in 1983. In constant dollars the budget increased from 1972 to 1979, which was the all-time peak year, and then declined by 12 percent between 1979 and 1982. It advanced about 4 percent in 1983, but comparison of 1983 with 1973 discloses only a 5 percent increase in the constant dollar budget of the NIH during that decade.

This next slide depicts some of the mechanisms of expenditure of the NIH budget. In fiscal 1982, roughly half--actually 52 percent--of the total NIH budget was in R01 and P01 research projects; 4 percent was in training, 12 percent was spent intramurally at the NIH. The 1983 budget proposed by the President in his State of the Union Address over a year ago contained a 2.9 percent increase in the NIH budget over the previous year. Congress did not actually pass a 1983 budget, but the continuing resolution contained a 9.9 percent increase over 1982 for the NIH. Parenthetically, the process of budgeting by a continuing resolution has become almost a way of life. The NIH has had four budgets in the last 11 years and 26 continuing resolutions. The next slide please.

One of the responses of NIH to the constrained budgets of the past decade has been to protect the category of investigator-initiated research grants. A series of decisions has resulted in a gradual shift of resources into the research grant category at the expense of contracts and to some extent some of the expense of training. Year by year since about 1974 a somewhat larger fraction of the extramural budget has been assigned to the research grant

category. Because of the fluctuation that occurred in the number of new and competing awards made annually in spite of these shifts (from a low of 2,900 to a high of 5,900 during the 1970s), in 1980 NIH developed a broad policy of stabilization of its support for extramural and intramural research and training. The policy has evolved, however, into a narrower objective of funding 5,000 new and competing awards and 10,000 traineeships and fellowships per year. The original policy was intended to stabilize not only the research grant category but other mechanisms as well. But it was assumed that the NIH budget would grow at a rate at least equal to inflation, and that did not happen between 1979 and 1982.

The slope of the increase of funds in the research grant category is such that it would reach 100 percent of the extramural budget in about 1993. That is, of course, unlikely to occur, but that projection underscores the need for some modification of the stabilization policy. But even with the shift of resources into the research grant category, funding for research grants has become very tight. Last year and this year, we expect to fund between 30 and 35 percent of approved awards. The paylines (priority scores) of funded grants tend to be very low. I point out, however, that the new investigator has always fared quite well and continues to do so. Of the new and competing awards, roughly 50 percent are new; and of the new, roughly 50 percent are made to first-time applicants. Overall, about 10 percent of our 16,000 awards are made to first-time applicants. These figures agree well with historic data, and should be encouraging to young scientists.

Now a few words about the 1984 budget. In order for you to understand it, I would like (next slide) to give you some idea of the time frame in which budgets are constructed. Notice that the formulation of the 1984 budget began in 1982. It proceeded throughout that entire calendar year and evolved through

several stages: development within individual Bureaus, Institutes, and Divisions of NIH; integration in the Office of the NIH Director; submission to the Public Health Service, integration of the NIH budget with those of other agencies within the PHS, presentation of the PHS budget to the Department of Health and Human Services, presentation of the HHS budget to OMB, and the integration of the Department's budget into the budget presented by the President. It is a very lengthy process and begins long before the budget of the previous year is known. In this case congressional action on the 1983 budget took place late in the course of construction of the 1984 budget. The basis for the 1984 budget would normally have been the continuing obligations generated by actions of the previous year. But at the time the 1984 budget was submitted, only those of the 1982 budget were known. Thus the 1984 budget was predicated upon the President's projection for the 1983 budget, not on the 1983 continuing resolution which came along very much later in this process. Because the continuing resolution for FY 1983 provided a very substantial increase for the NIH budget and thereby generated additional commitments for 1984, there were numerous discussions as to adjustments that might be allowed in the construction of the final 1984 budget. Decision on that issue was made rather late--in fact, just a short time before the President was to announce his 1984 budget plan. The final decision was that the 1984 budget for NIH would be based on the 1983 President's budget, not on the level of the continuing resolution. On that basis we projected funding 3,674 new and competing awards in 1984. The budget announced in January was considered a tentative budget. The short fall between funding 3,674 and 5,000 new and competing awards was $158 million.

Secretary Schweiker resigned on February 4. Before he left office he secured a letter from the Administration reaffirming the policy of funding

5,000 new and compting awards in 1984. The possibility that additional funds might be forthcoming to meet that obligation was to be the subject of additional negotiations with OMB.

In late March the Administration decided that we should fund 5,000 new and competing awards within the original budget. Therefore, a number of budgetary shifts were required to create the funds necessary to award 1,326 additional research grants. One decision was to reduce the average cost of these grants somewhat more than had initially been envisioned. This decision reduced the short fall to about $140 million. The downward negotiations proposed, although fairly heavy, are not outside historic trends. There is an average reduction of 20 percent between the requested award level and that recommended by the study section. That percentage decrease has been fairly constant for more than a decade. We have proposed an average additional reduction of 10 percent between the recommended level and the actual award level. Historic reductions at this step have ranged from 3 to 10 percent in the past decade. We have proposed a 6 percent reduction of the recommended level of the noncompeting award. That is a little above historic figures which have ranged from 1 to 4 percent.

In order to generate the additional $140 million substantial shifts were required from other mechanisms. About $53 million has been transferred from the category of comprehensive and specialized research centers. Under this proposal most of the centers that come up for renewal this year will not be funded. In addition, we have transferred about $25 million out of the Biomedical Research Support Grant category. The BRSG is an award made to research intensive institutions for such needs as purchase of shared instruments or support of young investigators and pilot research projects. We have proposed about a 50 percent reduction in the size of that award to the

eligible schools. There are also many smaller transfers, such as a reduction of $5 million in research training, chiefly generated by the decision not to increase stipends in 1984. About $20 million has been moved out of contracts by reducing from 18 to 5 the number of clinical trials we would initiate in 1984. Another $5 million was transferred out of intramural research. During hearings on these budgets in the past months, first in the Senate and then in the House, a great many questions were raised about the wisdom of this approach to funding. The budget was called a "sleight of hand" budget in the Senate. In the House many congressmen decried the damage that might be effected by these shifts. Nevertheless, this is an illustration of the tyranny of priorities. With the decision to give primacy to the investigator-initiated research grant, which is the central element of our research mechanisms, funds for other mechanisms, also important but of slightly lower priority, will have to be cut back.

In the final few minutes I would like to discuss some needs of biomedical science that go beyond the 1984 budget and constitute a continuing agenda for the future. This unfinished agenda has at least four elements. One is the overall level of research funding. We are now supporting only about one-third of approved grant applications. Most Institute Directors feel we should be funding about one-half, and that at present we are failing to support some excellent science. The shortfall there is $400 million a year. The next sub-category is that of instrumentation. We have estimates of the unmet need in the category of larger shared instruments. That is about $100 million, or $20 million a year for 5 years. We do not have a precise estimate of the shortfall for purchase of smaller instruments, which are usually components of the routine grant application. The third category is research facilities. Between 1962 and 1968, NIH spent about $50 million a year in matching fund programs for

the construction of general research facilities. That program ended in 1969. The only construction funded with NIH money since then has been in the cancer program, plus a small amount recently by the Eye Institute. Consequently, many of these original facilities are now 15-20 years old and in need of modernization. In addition there are new needs, such as facilities to house toxic wastes until they can be disposed of. The fourth category is the general area of training. As you may have noticed from an early mechanism slide, there was a time we were assigning about 12 percent of the extramural NIH budget to training. Currently that figure is under 5 percent. The effects of cutbacks of training support are not immediately known but will become visable five or ten years later.

I have mentioned these as four areas of concern that must be addressed by NIH, as well as by all of you in this room and other public groups through the political process in the years ahead by concerted, intelligent presentation of the needs, not for the benefit of the scientist, but because resolution of these matters is essential to the progress in improvement in health and the continued conquest of the major diseases that plague mankind.

Thank you very much.

A WORLDWIDE PROBLEM IN MEDICAL RESEARCH*

by

James B. Wyngaarden, M.D.**

Before we begin, let me thank Anne Simmonds and the Organizing Committee for the invitation to participate in this symposium. Previous speakers have sketched their backgrounds so as to identify the perspectives they bring to this meeting, and perhaps I should do the same. I am presently Director of the National Institutes of Health in the United States, a position I have held for just over one year. Previously I was a faculty member at Duke University for 25 years, the last 15 as Chairman of the Department of Medicine, a large department heavily involved in research, with a critical dependency on outside funds for support of research and training, including the salaries of faculties engaged in these activities. I am quite familiar with the problems of unstable careers of both young faculty and mature nontenured faculty members, both from the standpoint of the Department Chairman in the University and of the Director of the NIH, which is the largest source of funds for support of research and research faculty in the universities.

The subject of my address, "A Worldwide Problem in Medical Research," has multiple dimensions, but central to it is the stability of university-based research--stability of financial support for established investigators and for the continuous production of well-trained medical scientists.

In her letter inviting my participation in this symposium, Anne Simmonds summarized her views of the need for a serious discussion of the status of the

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research enterprise, particularly of the way in which academic research is organized in Britain. Her concerns are equally applicable to the United States.

As background for my remarks, permit me to restate the points she made:

1. Present and foreseeable constraints on the economy dictate that the basic machinery for financing and conducting research be as effective as possible.

2. The current financial situation is producing changes within the universities, possibly threatening the dual support system.

3. Growing recognition of the contributions of academic research to all segments of national life and economy is accompanied by the realization that today's research in every sphere requires teams of full-time trained professionals--that it can no longer be solely the part-time occupation of the academic teaching force.

4. The present system results in an 80 percent turnover of research personnel every two to three years, offers little training and incentive for the young graduate, and is a poor investment for all concerned.

Ironically, these questions about the support of university-based research are becoming acute here in Britain, as in the U.S. and perhaps elsewhere as well, at a time when the basic science knowledge in biology and medicine is expanding at an awesome rate. The stock of usable knowledge is at an all-time high and the opportunities for successful application of that knowledge to unsolved problems of health and disease have never been brighter. In that application the joint participation of physician-scientists and Ph.D. scientists in a team effort is often highly productive. Yet the academic

structure rarely provides the same level of security to the non-physician members of the team in the clinical departments as to the physician members. A look at the evolution of the biomedical research enterprise in the U.S. may be useful as we compare some of our mutual problems and experiences.

In the United States the National Institutes of Health conducts or supports approximately two-thirds of all basic biomedical research and over one-third of all health-related research and development. After the end of World War II, the NIH began a period of rapid growth, the most significant period of which were the "Shannon years," 1955-68, when Dr. James Shannon was Director of the NIH. When he took office in 1955, the budget of the NIH was $82 million, and when he left office 13 years later the budget exceeded $1 billion. During his tenure there was a good supply of money but a relative paucity of information and ideas, as well as a relative shortage of trained scientists. Shannon and his associates, with the strong backing of Congress and in particular of Senator Lister Hill and Congressman John Fogarty, set about to build the scientific capability of the Nation. The NIH budget began to level off in 1968 and in the past decade the growth in support has been more apparent than real. The 1979 appropriation of $3.2 billion represents an all-time high in purchasing power. Between 1979 and 1982, the constant dollar level fell by 12 percent, and then increased slightly in 1983. (SLIDE 1) However, the 1983 budget is only 5 percent above the 1973 budget in purchasing power. Thus, the level of funding for biomedical research in the United States has not kept pace with the ever-expanding scope of opportunities, nor is it now capable of supporting the cadre of talented scientists eager to do research.

Our Federal biomedical research program is built on a dual system, a combination of large Government laboratories operated by the NIH working side by side with more than a thousand nonfederal--mostly academic--laboratories

carrying out research supported by the NIH. The importance we continue to attach to the nonfederal or extramural component is illustrated by the distribution of the FY 1982 budget. (SLIDE 2)

The designers of the emerging biomedical research program nearly 40 years ago reasoned that the Federal support program should permit the degree of flexibility inherent in grants rather than contracts. As a consequence, it was decided that the principal mechanism to be used by the Government for the support of research should be grants made to the academic institutions, hospitals, and laboratories to carry out work proposed by individual investigators. These grants were designed to provide maximum freedom for investigators in the pursuit of answers to the questions presented as justification for the research support. Thus, the investigator-initiated research project grant came into being and it continues to be the main mechanism used by the NIH in carrying out its mission.

In the current NIH budget and the proposal for 1984 which we have recently submitted to the Congress, just over 50 percent of our funds are designated for these project grants. (SLIDE 3) A number of other funding mechanisms are used as well, including grants for the support of research centers of various types where, for example, multidisciplinary teams of researchers collaborate on specific disease problems and engage in related clinical demonstration and research training activities.

We use contract awards for procurement of specific research services and for the conduct of large clinical trials where it is important that uniform research protocols be followed by a number of cooperating investigators and institutions. In addition, about $167 million of our current budget is used for the support of research training. Almost 10,000 trainees are being

supported while in preparation for a career in biomedical research, through a system of individual fellowships and institutional training grants.

For the moment, however, permit me to focus on the investigator-initiated research grant. With only minimal restrictions, any investigator may apply for a research project grant to carry out specified research that is related to the overall mission of the NIH. As a result, some 15,000 to 20,000 research grant applications are received and reviewed by the NIH each year. It has never been possible for the agency to fund all grants considered worthy of support. At this time, we are able to fund only about one-third of the approved applications each year.

For more than 30 years, we have employed a peer review system to assist us in making the crucially important choices among grant applications. In this process, we rely almost exclusively on members of the nonfederal scientific community. Study sections, organized along disciplinary lines, are asked to assess the scientific merit and technical feasibility of grant applications and to assign to each a rating or priority score. In later considerations the score becomes the single most important factor when the final decision is made to fund or not to fund.

A second review is conducted by the National Advisory Council of the prospective funding Institute. The councils are established by law and include in their membership not only scientists but public members as well. In the councils, additional judgments are made on the basis of the program concerns of the Institute. Under our authorizing statutes, no grant may be awarded that has not been recommended by the National Advisory Council of the funding Institute. The average grant runs from three to four years and, currently, the funding for the average grant amounts to $120,000 per year. About two-thirds

of that amount is for the direct costs of the project which include salary support for the investigator and technical personnel, and funds for equipment, animals, supplies, and professional travel. About one-third goes to the institution for indirect costs of research, chiefly overhead.

Salary support, as a component of the research grant budget, has evolved through several stages in the past 30 years. Initially, no salary support of faculty-level investigators was included in the grant, largely upon the advice of the universities which were concerned about conflicts of loyalty and dedication. The first departure from this policy involved requests for summer salaries for faculty who technically were on nine-month university appointments, and who wished to continue their Federally supported research projects during the summer. Next came requests for salary support for released time during the academic year, to enable the investigator to devote a larger share of time to research and to permit the institution to use the original salary component to hire temporary instructors or clinicians. Gradually this concept has receded, and in its place has come a dependence upon the research project dollar for the entire portion of faculty salary corresponding to the time and effort devoted to the research project. I should, in fairness, mention that there is extreme variability in the patterns I have traced among the academic institutions in the United States. At one end of the spectrum are institutions that seek reimbursement for faculty salary time, including that of tenured members, for virtually every minute spent in research, and at the other are institutions that request no reimbursement at all for research time of tenured faculty members. Many institutions have developed parallel tracks of research-oriented faculty, some with full tenure, others with modified tenure that depends upon the availability of outside funds, and indeed others with a "research track" with no tenure at all, in which the investigators, even rather

senior ones, are virtually guest workers in the institution as long as external funds are available.

This inequitable "non-system" caused rather minimal concern when research funds and support dollars were relatively freely available. But with the budgetary constraints of the past decade, the concerns of non-tenured faculty have understandably increased. The NIH has attempted to make a positive contribution to this problem by stabilizing the number of new and competing research grant awards that are made each year. For the past several years, it has been our policy to maintain the budget assigned to project grants at a level which would permit us to make approximately 5,000 new or competing awards annually. One of our great concerns is the possible adverse effect of a decline in the availability of grant funds on young scientists. The stabilization policy has helped to insure a steady entry of emerging scientists into the biomedical research endeavor. Currently, 50 percent of all new awards and 10 percent of our total portfolio of over 16,000 awards are made to first-time applicants. These numbers agree well with historic figures, and arise solely on the basis of open competition, not because of any special protectionist policy of NIH toward first-time applicants.

The intense competition for research support has increasingly taken its toll of the investigator whose priority score is not at the very top. Furthermore, the professionalization of research activity has progressively selected against the M.D. scientist. Fifteen years ago the M.D. investigator had a better prospect of success in research applications than the Ph.D. applicant, but this is no longer true. (SLIDES 4 and 5) Since about 1974, applicants having both the M.D. and Ph.D. degrees enjoy the highest success rate, followed by those with the Ph.D., and then by those with just an M.D. degree, who are competing progressively less well.

The status of the physician-scientist has been a subject of interest to me since long before I came to the National Institutes of Health. The burgeoning of basic knowledge in the past decade has opened up vast opportunities for clinical research. Yet, comparatively, the number of physicians interested in applying themselves to the clinical research needs of the future is diminishing. (SLIDE 6)

Among the reasons cited for the declining interest of physicians in clinical research are the following:

- o The average medical school curriculum contains little or no opportunity for laboratory experience.
- o The debt load of medical students has grown enormously. While the average is about $19,000, debts as high as $30,000 upon graduation are not unusual.
- o The average NIH training stipend pays on the average $6,000 per year less than does clinical specialty training.
- o The growing sophistication of science and its professionalization in clinical departments requires that the recipients of even the finest medical education and residency training spend a substantial amount of additional time, as long as three years, obtaining the necessary skills to be successful in research.

Within the past few years, the NIH has developed several programs, in addition to its regular research training grants, that are designed to acquaint the physician in training with the excitement and possibilities of biomedical research.

1. Because medical curricula today have eliminated many of the laboratory exercises which once introduced students to research techniques, the NIH has

initiated a program of short-term training in health professional schools to expose students early in their professional studies to opportunities in research. The program now supports more than 1,100 students a year during vacation or off-quarter periods in approximately 70 schools of medicine, dentistry, pharmacy, and veterinary medicine. It is hoped that this will be an effective recruiting device for the future.

2. A second program providing an early research experience is a summer fellowship at the NIH offered to outstanding medical students throughout the country. Last year, 52 medical and dental student fellows selected from various institutions conducted laboratory research and attended lectures and seminars at NIH. This program continues as a part of an ongoing effort to attract promising young physicians into research careers.

3. A third initiative for attracting medical students into research is one often called the "post-sophomore fellowship." It is our view that a short-term exposure to research, although useful as an introduction, is less effective than a longer initial laboratory experience. Accordingly, the NIH in the summer of 1982 re-established a program for support of students who interrupt professional education for a full year of research training.

4. The newest addition to the career development award programs will be announced next month. The physician-scientist award will be supported by several of the NIH Institutes. The award is designed to provide five years of phased supervised research training with a heavy emphasis in basic science. The first few years of research training will be obtained in a basic science department. The award will carry a salary equivalent to that earned by a member of the institution's house staff with equivalent experience and will include $10,000 for research costs. The second phase undertaken at a more

independent level will have up to $20,000 available to cover research costs. At the conclusion of this five-year program, a young physician-scientist should be well prepared to compete for NIH research grant support.

We have not solved the role of long-term, non-tenured researchers in clinical departments, nor for that matter in basic science departments. Reference was made by a previous speaker to the relatively larger numbers of Ph.D.s in clinical departments in the United States than in Britain. The statement may well be correct, but in my experience the Ph.D.s with permanent positions in clinical departments in the U.S. are predominantly in the service roles--for example, clinical psychologists and sociologists in departments of psychiatry, audiologists in ENT departments, radiation physicists in radiology departments, and so forth. To be sure, some of the larger surgical departments will have units stably directed by Ph.D. scientists. But the great bulk of biomedical research conducted in clinical departments in the United States takes place in departments of medicine, in which it is unusual for Ph.D. scientists to have stable tenured appointments. In the department at Duke there were 160 full-time physician faculty, over half of whom had tenure. There were some 40 Ph.D.s in addition, only one of whom had tenure. That was a computer scientist whose financial tenure was shared by departments of medicine and surgery and the hospital.

In the event of failure of grant support for an investigator or a unit in a clinical department in the United States, interval support is frequently provided by the department until grant support can be reinstituted. Depending on resources, such interval support might last a few months, perhaps as long as a year or two in exceptional situations. But if external support can not be reestablished, the unit will likely be disbanded.

The intense competition for grant support at the level of NIH, which applies also to other agencies such as the National Science Foundation, the Veterans Administration, and private foundations, has led to a great increase in the number of amended or revised applications received at NIH. Last year over 25 percent of all grant applications submitted to NIH were amended applications, and this figure is roughly twice that of three or four years ago. There clearly has also been an increase in the choice of alternative careers. More physician-scientists at the advanced fellow or young faculty levels have changed plans and entered practice. There has been greater interest on the part of Ph.D. scientists in industry. And there has been a negative feedback effect upon the entry of graduate students and young physicians into research training, although this has been rather selective by fields.

In my statement, I have limited my remarks to the American experience for the simple reason that my intimate familiarity is limited to that domain. But it is clear that there is a worldwide problem in career stability and continuity for biomedical scientists. It is most acute for those investigators who do not secure permanent or tenured positions on university faculties or on the staffs of research institutes. But it also exists in the universities for tenured scientists whose research support is not forthcoming for whatever reason.

In closing, let me congratulate the organizers of this symposium for highlighting this worldwide problem and for bringing it to the attention of health research planners in official positions. We should mutually wish each other well as we address potentially ameliorating solutions.

Once again, thank you very much for inviting me to participate.

REMARKS*

by

James B. Wyngaarden, M.D.**

Mr. Chairman, let me say at the outset how pleased I am to be able to attend this meeting of representatives of the European Medical Research Councils (EMRC) and to report on the state of programs of the National Institutes of Health (NIH). As you know, I became Director of NIH just over one year ago, so this is my first opportunity to attend a meeting of the EMRC.

The NIH follows the activities of EMRC with great interest, particularly in the areas of toxicology, human reproduction, technology assessment, and the use of experimental animals. We continue to accord a high priority to international cooperation in biomedical research. Also, I should add that we anticipate no change in our long-standing policy of supporting excellent research applications received from scientists outside the United States, and particularly when there is some unique aspect to the research proposal that extends beyond similar projects that might be conducted within our own country. During fiscal year 1982 we supported about $62 million worth of research and related activities involving foreign countries. About half of this amount supported research grants and contracts outside the United States, and about half supported foreign scientists working within the United States or American scientists abroad and related travel expenses.

Today I will spend a few minutes talking about NIH programs and budget, and then briefly summarize NIH involvement in an issue that is a matter of

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great concern within the U.S. and one that is becoming an international problem--namely, the issue of Acquired Immunodeficiency Syndrome (AIDS). At the risk of repeating statistics you have already heard, I would like to take a look at how the NIH budget has changed during the last 25 years and the impact of these changes on NIH programs. As you know, NIH's main program growth came during the period of 1955-1968 when Dr. James Shannon was Director of the NIH. The budget when he entered office was $82 million, and when he left was over $1 billion. Since that time, growth has been much more modest. Between 1972 and 1983 there has been a 15 percent increase in constant dollars, but the growth of indirect costs during this period almost exactly consumed this increment so that the funds available to support the direct costs of research are essentially the same in 1983 as in 1972. The high water mark of the NIH budget was reached in 1979. The budget then fell by 12 percent in purchasing power between 1979 and 1982 but rose by 4 percent in 1983 for a net decrease of 8 percent. In short, the NIH budget has been essentially in a steady state for more than a decade. At the same time I should point out that NIH has fared better than many other agencies during this period of economic constraint, because of the high priority given this endeavor by both the Administration and the Congress.

A few other statistics may also be of interest. About 12 percent of our budget is spent in research conducted intramurally at the NIH, chiefly in Bethesda. Eighty-one percent of our budget is spent extramurally, chiefly in academic health centers and other institutions of higher education. Overall we classify 54 percent of the research that we support as basic, 37 percent as mission-oriented, and 10 percent as developmental.

Historically we have accommodated to the relatively constant budget of the past decade by shifting funds from other NIH mechanisms so as to support as

many excellent investigator-initiated research proposals as possible. These changes began in 1974, but were not articulated as a stabilization policy until fiscal year 1980 when we asked the U.S. Congress for sufficient funds to support a minimum of 5,000 new and competing research grants and 10,000 trainees. In 1974 about 63 percent of our extramural support was in the category of research grants; this year that fraction is 83 percent. The shift came at the expense of support for contracts, centers, clinical trials, research instrumentation, and facilities. Since our fundamental mission is the improvement of health and well-being, we must also emphasize prevention of disease and disability and make a special effort to see that scientific discoveries are transferred to medical practice as quickly as possible. As a consequence, we have continued to place particular emphasis upon research that is prevention oriented and upon technology transfer.

The stabilization policy has enabled us to dampen large fluctuations in support of new and competing research awards. In 1981 we supported 5,140 grants; in 1982, 5,027 grants; and the 1983 budget projects support of 4,914 new and competing grants awards out of a research grant portfolio of about 16,357. The 1983 budget will also support 9,969 research trainees. New scientists are entering the biomedical research enterprise at rates consistent with historic figures. About 50 percent of all new and competing awards go to first-time applicants, and about 10 percent of our entire grant portfolio of over 16,000 awards go to first-time applicants. This is a result of their ability to compete, not because of any protectionist policy for new applicants.

The President's proposed fiscal year 1984 budget is $4.077 million, representing a 1.8 percent increase over 1983. The Administration has instructed us to support 5,000 new and competing project grants and some 9,000

research trainees. In order to meet these goals we have had to make some rather drastic cutbacks in support of specialized centers and biomedical research support grants which contain flexible funds for use of research intensive institutions. In our budgetary hearings before the Congress which have just been concluded, there was strong indication in both the House of Representatives and the Senate that the Congress might add funds to the President's budget to make these cutbacks unnecessary.

We may have reached the limit of utility of the stabilization policy in its present form. Many Institute Directors feel that further shifts of funds into the research grant category would seriously limit their ability to meet other program goals and to maintain program balance. This year we are involving the Director's Advisory Committee in a review of the impact of our stabilization policy on all of NIH, and particularly on the extramural program. It is likely that the concept of stabilization will be modified, perhaps to set an upper limit of the percentage of our extramural budget that will be assigned to research grants.

Another continuing issue of concern is the training of sufficient numbers of investigators to maintain the vitality of research. Although there is currently an adequate supply of scientists in most fields, the proportion of physicians involved in biomedical research is diminishing. The success rate among applicants for grants has historically been about the same for investigators with combined M.D./Ph.D. degrees, Ph.D. degrees, or M.D. degrees. But since about 1974, there has been a progressive divergence with M.D./Ph.D. degree applicants competing most successfully, followed by Ph.D. applicants--both of which are well above the average--and then by M.D. applicants, whose success rate is steadily declining and is now far below the first two categories.

There are also fewer physicians interested in training in biomedical research. Of the 2,800 positions that the National Academy of Sciences recommends be devoted to clinical research training, only 1,900 are filled by M.D. trainees. The major barriers to attracting physicians include the income possibilities of practice, the length of subspecialty training programs, the lack of research experience during medical school training, the increasing complexity of science which in turn leads to a need for longer research training, the widening gap between laboratory and bedside, the educational debtload incurred by physicians which now averages $19,000 at the time of graduation, and the relatively low level of research training stipends which now average some $6,000 less than the equivalent house staff position in a hospital. There is also the apparent instability of federal commitment to research support, and the intense competition for research funding that physicians in training observe among the faculty of the medical schools.

In recognition of the increasing complexity and professionalization of biomedical research, we are instituting a new type of physician scientist training program which will provide support for 5 years of combined full-time research training and initial faculty support, with stipends well above the residency levels. The award will also include $10,000 to $20,000 per year for the costs of research. These training programs will enable young physicians to return to basic science departments for an initial period of two to three years and will provide some initial salary support for the first few years of an academic appointment. The program will start on a rather small scale, initially perhaps supporting about 400 trainees per year. We are also offering several programs of shorter term support at the medical student level designed to provide research experiences during off-quarters or elective years of the medical curriculum. We are hopeful that the combination of earlier introduction to

research and a more prolonged period of support for more intensive training in basic biomedical science will make a contribution toward repairing the perceived deficit in physician investigators in biomedical science.

Finally I would like to comment on a high priority research area of international interest, the Acquired Immunodeficiency Syndrome (AIDS). When the AIDS problem was recognized in early 1981, close liaison was established among the Public Health Service agencies in the U.S. with major responsibility in this area, each emphasizing its primary mission: the Centers for Disease Control (CDC), surveillance and investigation; the Food and Drug Administration (FDA), preventive measures related to blood collection and its use; and NIH, research into fundamental causes and clinical aspects of AIDS.

Since June 1981, when CDC initiated national surveillance, more than 1,400 cases of AIDS have been reported from 35 states and the District of Columbia and 88 cases from 16 foreign countries. Of the cases in the United States, 520 deaths (38 percent) have thus far occurred. Of the (101) AIDS cases diagnosed two or more years ago, 81 percent of the patients have died. Incidence by date of diagnosis has roughly doubled every six months since the second half of 1979, and is still rising.

As you know, current epidemiologic evidence identified several groups in the United States at increased risk for developing AIDS. Most cases (75.7 percent) have been reported among sexually active homosexual or bisexual men, primarily young (25-45) and urban. The second largest group (14.5 percent) of AIDS patients are heterosexual persons who are abusers of intravenous drugs such as heroin. A third group of AIDS patients (5 percent) is made up of Haitians, especially those who have entered the country in recent years. Other groups of AIDS patients are persons with hemophilia and no history of

homosexuality, intravenous drug use, or Haitian background (0.9 percent) and those with no apparent characteristics of the other risk groups (3.9 percent).

During fiscal 1983, the NIH will spend approximately $9.5 million on research projects specifically related to the AIDS problem. There is also presently before the Congress a bill for a supplemental appropriation of an additional $9.5 million for NIH during the current fiscal year. These funds for highly focused and targeted research are superimposed on a very large base of support in such areas as immunoregulation, viral agents, opportunistic infections, and blood purification and storage. NIH research programs in immunosuppression and related fields, generally relevant to but not specifically targeted upon the AIDS problem, amount to about $200 million per year. There is also a potential animal model of this disorder. Two primate colonies in the United States have developed acquired immunodeficiency states, unrelated to any known cause. In both colonies, young monkeys fall prey to opportunistic infections chiefly of the gastrointestinal tract. In this respect their illness resembles the clinical syndrome seen in Haiti somewhat more closely than that seen in the United States. In Haiti the AIDS patients tend to develop gastrointestinal candidiasis or other parasitic and bacterial enteritides, whereas in the United States opportunistic infections of the lung are more common.

The NIH recently convened a meeting of biologists with expertise in the isolation of new infectious agents. It was their view that a viral etiology of AIDS was probable. Leading candidates were thought to be an animal virus perhaps recently accommodated to man, or a new mutant of some known virus. Recent research has suggested some relationship between AIDS and T-cell leukemia virus in at least some victims. Until the etiology of AIDS is understood, it will continue to be a health threat in the United States and

throughout the world. We consider it critical that the international scientific community work together in this important endeavor and urge maximum attention through your Councils to this problem.

Remarks of
Dr. James B. Wyngaarden
EPMC Expanded Forum
June 13, 1983

Concern about protecting human subjects in research is not new to us at NIH. Thirty years ago when the Clinical Center opened, NIH instituted the first Federal policy requiring prospective independent ethical review of all research proposing to involve normal volunteers under Clinical Center auspices.

In the early sixties, Dr. Jim Shannon, always amazing in the clarity of his foresight, recognized the need for NIH to be the pacesetter in establishing ethical standards for clinical research. Dr. Shannon took the leadership in developing a set of ethical standards that were intended to be every bit as exacting in protecting research subjects as NIH's scientific standards. He commissioned a study in 1962 at the Boston University Center for Law and Medicine to examine possible measures to assure adequate protections for human research subjects. Then, after further review and recommendations by a blue ribbon panel of NIH researchers, Dr. Shannon proceeded to win endorsement of the proposed measures as the policy for the entire Public Health Service. The PHS adopted it as policy in 1966.

I believe we have decisive evidence of the validity of the vision that shaped that early policy. The basic features of the policy--review by an independent committee, informed consent, a favorable risk/benefit ratio and adequate safeguards for subjects--these basic features remain today. The policy has been policy of the Department of Health and Human Services for over a decade and the basis for HHS regulations since 1974; it forms the

basis of the new proposed model Federal policy; its main features have been endorsed and adopted throughout the world, by the World Health Organization and the Council of International Organizations of the Medical Sciences. Two Congressionally mandated commissions have studied and favorably reported on it; it has been reviewed and discussed in scholarly circles and public forums for nearly two decades. These subsequent initiatives and the thoughtful comments of critics and supporters have enriched the basic features set out by the original NIH proposal. But the fundamental soundness and workability of the policy have been reaffirmed repeatedly and public agencies and private institutions have adopted it widely to insure the protection of individuals who participate as subjects of research.

That cannot help but seem impressive. Yet, in a way, to me it is not surprising. Each iteration has reflected the research community's conviction that excellent science can and must go hand in hand with the conduct of research that is ethically sound and professionally responsible. Our basic goal has always been to foster the cure and prevention of human illness while minimizing any possible risk and distress to research subjects and ensuring their willing and enlightened cooperation in this essential activity. Hence, it is not surprising that a policy based on this principle should endure and find wide acceptance.

I have touched on the role of NIH and other PHS program administrators in protecting human subjects to put this topic in the proper perspective. We at NIH have a distinct leadership role in the U.S. research community. We support the work of a

GREAT MANY SCIENTISTS AND THUS ARE IMMEDIATELY INVOLVED IN THEIR ACTIVITIES. OUR ROLE AS A FEDERAL AGENCY SUPPORTING SCIENCE ENABLES US TO SEE SCIENCE AS PART OF A BROADER FLOW WHICH FORCES US INTO THE SOMEWHAT LESS TRANQUIL CURRENTS OF POLITICAL COMPETITION FOR RESOURCES. IN ITS OWN HOME WATERS THE CRAFT OF BIOMEDICAL AND BEHAVIORAL RESEARCH CAN TACK AND LUFF SLEEKLY. BUT IN THE CHOPPY SEAS AND CAPRICIOUS WINDS OF POLITICS, WE AT NIH ARE OFTEN ASKED TO ACT AS PILOTS TO SKIRT SHOALS AND REEFS.

THE ETHICAL STANDARDS ARTICULATED ORIGINALLY AND THEIR SUCCESSIVE REVISIONS HAVE INTRODUCED NEW SENSITIVITY TO THE PROTECTION OF RESEARCH SUBJECTS INTO EVERY STEP OF THE PROCESS, FROM PREPARATION OF RESEARCH PROPOSALS THROUGH INSTITUTIONAL POLICIES AND REVIEW AT THE NATIONAL LEVEL. BUT THE TASK, LIKE THE TASK OF ASSURING ADEQUATE RESOURCES FOR RESEARCH AND THE TASK OF ADVANCING KNOWLEDGE, IS NOT EVER COMPLETE. HENCE, WE STRIVE TO FIND WAYS TO REVISE AND STRENGTHEN OUR PROCEDURES PERIODICALLY BECAUSE OUR JOB AT NIH IS TO SUPPLY UNEQUIVOCAL GUIDELINES TO MONITOR CLINICAL RESEARCH AND TO DO ALL IN OUR POWER TO PREVENT CLEAR ABUSES. WE ARE EXPECTED TO DEMONSTRATE THAT GOOD SCIENCE AND HIGH STANDARDS OF ETHICS ARE CLOSELY LINKED.

I SAY THIS TO REMIND YOU THAT PROCEDURES ARE MEANS TO AN END; THEY ARE NOT AN END IN THEMSELVES. THE PROCEDURES GET ALL OF US TO THINK ABOUT OUR RESPONSIBILITIES FOR PROTECTING HUMAN SUBJECTS WHILE WE ENGAGE IN THE TASK OF ADVANCING HUMAN KNOWLEDGE. PROCEDURES ARE THE OPPORTUNITY AND THE MANDATE TO EXERCISE PROFESSIONAL JUDGMENT. THEY FOCUS AND ENCOURAGE CAREFUL THINKING ON OUR PART ABOUT THE RESPONSIBILITY WE HAVE AT NIH TO SAFEGUARD SUBJECTS.

To the non-scientific world, the procedures demonstrate systematic, careful, judicious measures in our stewardship of the rights and welfare of individuals. But, let me emphasize, procedures are no substitute for professional judgment.

Potential hazards to human subjects are sometimes the price of doing research intended to benefit them directly or to add to our understanding of human disease. This is true in large trials where hundreds of individuals may be randomized with no infallible indicators of which medication or intervention might be more or less beneficial in an individual for quite unforeseeable and idiosyncratic reasons. It is also true in small pilot studies where therapeutic innovations are tried on a small, select subject population.

However, the presence of risk places a special demand on us that only the highest quality research be conducted. For example, in large clinical trials, especially collaborative trials, program administrators must meet this demand in the concept and planning stage. The hypothesis selected must be based on an assessment that an intervention is suitable for adoption (or retention) in the body of accepted medical practice. Often this assessment can only be made after wide consultation in the field through such mechanisms as advisors or consensus development conferences. Subsequent steps will involve careful design incorporating the best statistical techniques to insure a proper sample size. Whatever elements are incorporated in the design are to be selected to increase the probability of definitive results.

So, too, the selection of centers or investigators to carry out the trial will require vigorous scientific review and site visits to insure that the research is of the highest quality.

The importance of insuring that only the highest quality of research is acceptable in clinical trials springs from our concern for the individuals who will be subjects of the research, and for the society that stands to benefit from the knowledge obtained. When hazards to individuals involved in doing the research, there is a special need to insist on the quality of research design and the high probability of definitive answers. It is, I submit, axiomatic that in clinical research, to be unscientific is to be unethical. And if our scientific procedures are to be rigorous and precise, so too must our internal administrative procedures be uncontestably systematic, careful, judicious.

I believe we can be justifiably proud in the way NIH has contributed to and promoted biomedical and behavioral research. In furthering advances in biomedicine, we have fostered the wide acceptance of scientific methodology as a means to cure and prevent disease and to improve the human condition. There is equal reason to single out the NIH leadership role in demonstrating that the advance of human knowledge need never encroach on human dignity and well-being.

As I stated earlier, procedures are not a substitute for professional judgment but the opportunity for its exercise. I believe the substance and meaning which transform the procedures comes from your application of them as part of your responsibilities in carrying out the NIH mission. The procedures were developed

over the course of time by you and your colleagues to facilitate the administration of science. Science administration is not always heady and exciting, but it is made up of experience, ingenuity, wisdom, and reflection. The "moment of truth" comes when the procedures help insure the integrity of the NIH system for protecting human research subjects. The integrity of that system is more essential than the particular interest of any specific scientific pursuit or the special interest of any group. The integrity of that system is evidence of the integrity of scientific research. We can be and need to be eloquent in defense of that integrity when it is maligned or unfairly criticized. But our actions are more eloquent than our words. They are the "moment of truth" of the principle that excellent science and high standards of ethics are closely linked.

Dr. Raub, Dr. McCarthy and other OPRR staff, and some of your colleagues will review for you this morning and in follow-up sessions the main points of the up-dated NIH policy for review and award of grants involving human subjects. Your being here reassures me of your strong commitment to NIH ideals. I know this session will assist us all in carrying out the mission of NIH.

BIOMEDICAL RESEARCH AND FEDERAL POLICY
CURRENT INITIATIVES AND CONSTRAINTS: WHAT THE FUTURE HOLDS*

by

JAMES B. WYNGAARDEN, M.D.**

SINCE THE 1940s, THE PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH HAVE CONSTITUTED A PRIME EXPRESSION OF FEDERAL POLICY ON BIOMEDICAL RESEARCH IN THE UNITED STATES. AS SHAPED BY SUCCESSIVE ADMINISTRATIONS AND THE CONGRESS, THAT POLICY HAS FROM THE BEGINNING ENCOURAGED DIVERSITY AND EXCELLENCE IN HEALTH RESEARCH; IT HAS RELIED ON THE SCIENTIFIC COMMUNITY ITSELF TO IDENTIFY THROUGH A COMPETITIVE PEER REVIEW PROCESS THE IDEAS AND INVESTIGATORS MOST WORTHY OF SUPPORT. IN THIS WAY, PUBLIC FUNDS INVESTED IN BIOMEDICAL RESEARCH HAVE SUPPORTED THE MOST CREATIVE IDEAS AND ENERGIES IN THE AMERICAN HEALTH RESEARCH COMMUNITY—A WEALTH OF IDEAS WHOSE RANGE HAS FAR EXCEEDED THOSE THAT COULD HAVE BEEN GENERATED BY ANY SINGLE COMMITTEE, BOARD, COUNCIL, OR LABORATORY.

BECAUSE THE NIH IS THE PRINCIPAL CREATION OF PAST AND PRESENT FEDERAL POLICY ON BIOMEDICAL RESEARCH, I BELIEVE IT APPROPRIATE TO MAKE THE AGENCY THE CENTRAL FOCUS OF MY GENERAL DISCUSSION OF SUCH POLICY.

OUR BROAD CHARTER IS CONTAINED IN SECTION 301 OF THE PUBLIC HEALTH SERVICE ACT OF 1944 WHICH CONTINUES TO BE OUR GOVERNING STATUTE. THE SECTION CONSTITUTES A DIRECTIVE TO ". . . CONDUCT . . . AND ENCOURAGE, COOPERATE WITH, AND RENDER ASSISTANCE TO OTHER APPROPRIATE PUBLIC AUTHORITIES, SCIENTIFIC INSTITUTIONS AND SCIENTISTS IN THE CONDUCT OF AND PROMOTE THE COORDINATION OF RESEARCH, INVESTIGATIONS, EXPERIMENTS, DEMONSTRATIONS, AND STUDIES RELATING TO THE CAUSES, DIAGNOSIS, TREATMENT, CONTROL, AND PREVENTION OF PHYSICAL AND MENTAL DISEASES AND IMPAIRMENTS OF MAN . . ."

IN LESS FORMAL LANGUAGE, THE COMMITTEE REPORT THAT ACCOMPANIED THE ACT STATED THAT THE PURPOSE OF THE LEGISLATION WAS TO "CONSOLIDATE AND RESTATE THE BASIC AUTHORITY OF THE PUBLIC HEALTH SERVICE IN THE WHOLE FIELD OF RESEARCH SO AS TO GRANT IN CLEAR AND UNMISTAKABLE TERMS BROAD AUTHORITY TO CARRY ON INVESTIGATIONS THROUGH ITS OWN PERSONNEL AND TO COOPERATE AND ASSIST IN THE INVESTIGATION BY OTHERS OF ALL PROBLEMS BEARING ON THE PHYSICAL AND MENTAL HEALTH OF OUR PEOPLE."

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*Lecture before the Health Policy Study Group at the University of Texas Health Science Center, Houston, Texas, June 23, 1983

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BY THE MID-FIFTIES, THE OVERALL BUDGET OF THE NIH HAD GROWN TO $82 MILLION, OF WHICH MORE THAN $54 MILLION WAS EXPENDED IN GRANTS. THE STAGE HAD BEEN SET FOR A RAPID AND MASSIVE EXPANSION OF NIH AND ITS PROGRAMS. DURING THE FOLLOWING DECADE, THE TOTAL NIH BUDGET GREW TWELVEFOLD AND EXPENDITURES FOR GRANTS FIFTEENFOLD.

THIS PERIOD OF SPECTACULAR GROWTH CAN BE VIEWED AS THE RESULT OF A FIRM ACCEPTANCE BY THE FEDERAL GOVERNMENT OF THE RESPONSIBILITY FOR SUPPORT OF BIOMEDICAL RESEARCH--BASIC RESEARCH, IN PARTICULAR.

IT WAS FORTUNATE THAT DURING THE PERIOD OF ITS EXPLOSIVE GROWTH FROM 1955 TO THE LATE SIXTIES, THE NIH WAS DIRECTED BY AN UNUSUALLY ABLE, SENSITIVE, AND STRONG LEADER, DR. JAMES A. SHANNON. UNDER DR. SHANNON, MANY OF THE CURRENT MECHANISMS OF SUPPORT OF BIOMEDICAL SCIENCE WERE ESTABLISHED, CONFIRMED, AND EXTENDED. THEY HAVE SERVED THE NIH AND THE SCIENTIFIC COMMUNITY WELL. JIM SHANNON INSISTED THAT THE CONGRESSIONAL MANDATE TO CONDUCT RESEARCH IN CANCER, HEART DISEASE, AND ARTHRITIS, FOR EXAMPLE, BE INTERPRETED BROADLY. HE REALIZED THAT THE SCIENCE BASE WAS NOT SUFFICIENT TO PERMIT A FRONTAL ASSAULT ON THE DISEASES THEMSELVES. HE SET ABOUT TO BUILD THE RESEARCH CAPABILITY OF THIS COUNTRY THROUGH THE INTRAMURAL PROGRAM AT BETHESDA AND THROUGH A SUBSTANTIAL EXPANSION OF THE MECHANISMS OF GRANTS-IN-AID TO INSTITUTIONS.

CORRELARY OBJECTIVES INCLUDED THE STRENGTHENING OF THE INSTITUTIONS IN WHICH BIOMEDICAL RESEARCH WOULD BE DONE AND THE DEVELOPMENT OF TRAINING MECHANISMS THAT WOULD INSURE A CONTINUING SUPPLY OF COMPETENT SCIENTISTS DRAWN FROM THE BEST AND THE BRIGHTEST YOUNG MINDS IN THE UNIVERSITIES. TOGETHER WITH HILL BURTON MONEY FOR CLINICAL FACILITIES, NIH CONSTRUCTION FUNDS FOR RESEARCH FACILITIES MODIFIED THE TOPOGRAPHY OF ACADEMIC MEDICAL CENTERS AND INDIRECTLY GREATLY STRENGTHENED MEDICAL EDUCATION IN THIS COUNTRY.

IN 1982, THE FEDERAL GOVERNMENT CONTRIBUTED ABOUT 54 PERCENT OF THE SUPPORT FROM ALL SOURCES FOR HEALTH-RELATED RESEARCH AND DEVELOPMENT IN THIS COUNTRY. THE NIH BUDGET ACCOUNTS FOR ALMOST 70 PERCENT OF THE TOTAL FEDERAL INVESTMENT. FOUR-FIFTHS OF THE EXPENDITURES OF THE AGENCY GO TO THE SUPPORT OF BIOMEDICAL RESEARCH CONDUCTED IN UNIVERSITIES, PRIVATE LABORATORIES, HOSPITALS, AND OTHER SUCH INSTITUTIONS.

FOR DECADES, THE MAIN NIH MECHANISM OF RESEARCH SUPPORT HAS BEEN INDIVIDUAL PROJECT GRANTS FOR STUDIES PROPOSED BY NONGOVERNMENT SCIENTISTS. JUST OVER ONE-HALF OF THE NIH BUDGET CURRENTLY IS USED FOR THE SUPPORT OF SUCH INVESTIGATOR-INITIATED PROJECTS.

WITHOUT AN APPRECIATION OF THE SOCIOLOGY OF SCIENCE, ONE MIGHT QUESTION THE WISDOM OF MAKING THE INVESTIGATOR-INITIATED GRANT PROJECT THE KEYSTONE OF A NATIONAL RESEARCH EFFORT. IN USING THIS MECHANISM, WE ARE UTTERLY DEPENDENT UPON THE VOLUNTARY SUBMISSION BY INDIVIDUAL SCIENTISTS OF NEW RESEARCH IDEAS. IN ONE SENSE, IT IS THE FREE ENTERPRISE SYSTEM TAKEN TO THE EXTREME. THE NIH HAS LITTLE OR NO CONTROL OVER THE RANGE OR NATURE OF THE IDEAS SUBMITTED TO IT FOR POSSIBLE FUNDING. YET, THIS VERY LACK OF CONTROL IS THE SOURCE OF THE AGENCY'S ABILITY TO TAP THE BEST IDEAS OF THE BEST MINDS IN THE NATION.

CERTAINLY, NO ONE SCIENTIST, NO MATTER HOW SOPHISTICATED OR EXPERIENCED, NOR ANY PANEL OF DISTINGUISHED SCIENTISTS, COULD HAVE THE INSIGHT AND CREATIVE ABILITY TO PRODUCE THE ARRAY OF RESEARCH PROPOSALS SUBMITTED TO THE NIH. (SLIDES 1 AND 2)

THE QUESTION MIGHT BE ASKED, "IF THE INVESTIGATOR-INITIATED GRANT IS SO PRODUCTIVE, WHY DOESN'T NIH DEVOTE ALL OF ITS FUNDS AVAILABLE FOR EXTRAMURAL RESEARCH TO THAT MECHANISM?" THE ANSWER IS THAT A NUMBER OF VITAL RESEARCH ACTIVITIES REQUIRE OTHER MECHANISMS; FOR EXAMPLE, LARGE CLINICAL TRIALS. USUALLY THESE TRIALS ARE CONDUCTED SIMULTANEOUSLY AT A NUMBER OF CENTERS SPREAD ACROSS THE COUNTRY. TO ASSURE COMPARABILITY AND VALIDITY OF THE FINDINGS COMING FROM THE VARIOUS SOURCES, IT IS NECESSARY THAT A UNIFORM PROTOCOL BE RIGIDLY FOLLOWED AT EACH OF THE CENTERS. IN THIS INSTANCE, CREATIVE VARIATIONS FROM THE AGREED UPON RESEARCH PLAN WOULD BE DESTRUCTIVE. SO THE USUAL MECHANISM FOR THE SUPPORT OF CLINICAL TRIALS IS A CONTRACT. SPECIALIZED AND COMPREHENSIVE CENTERS REPRESENT ANOTHER MECHANISM FOR ACCOMPLISHING NIH'S PURPOSES. SUCH CENTERS SUPPORT RESEARCH ON THE CAUSES, PREVENTION, AND TREATMENT OF SPECIFIC DISEASES, AND DEMONSTRATION OF NEW METHODS OF TREATMENT.

SUBSTANTIAL FUNDS ARE ALSO DEVOTED TO RESEARCH TRAINING. BECAUSE OF THE CENTRAL RELATIONSHIP OF TRAINING TO THE FUTURE OF BIOMEDICAL RESEARCH, I WILL IN A MOMENT DISCUSS IT AT GREATER LENGTH.

WHILE, AS I HAVE SAID, THE NIH IS ESSENTIALLY NONDIRECTIVE WITH REGARD TO ITS EXTRAMURAL PROGRAM, THERE ARE OCCASIONS WHEN WE ATTEMPT TO STIMULATE THE INTEREST OF INVESTIGATORS IN CERTAIN AREAS OF RESEARCH. CURRENTLY, FOR EXAMPLE, WE HAVE ISSUED FORMAL REQUESTS FOR APPLICATIONS ON SUBJECTS RELATED TO ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS). MUCH OF THE IMMUNOLOGICAL RESEARCH WHICH WE HAVE SUPPORTED THROUGH THE PAST YEARS HAS A DIRECT BEARING ON THIS DISTURBING NEW PROBLEM AND FORMS AN IMPORTANT BASE FOR FURTHER STUDIES, BUT THERE IS AN URGENT NEED TO FOCUS ON THE PARTICULAR MANIFESTATIONS OF THE BREAKDOWN OF THE IMMUNE SYSTEM ASSOCIATED WITH AIDS. INTENSIVE EFFORT IS BEING DEVOTED TO THE PROBLEM OF IDENTIFYING THE CAUSATIVE AGENT OF AIDS AND THE POSSIBLE MEANS OF ITS

TRANSMISSION, AND WE HAVE CALLED UPON THE RESEARCH COMMUNITY TO FOCUS ON THE PROBLEMS AND TO SUBMIT NEW IDEAS FOR RESEARCH.

WITHIN THE LAST HALF CENTURY, THE AMERICAN PUBLIC HAS A NEW APPRECIATION OF THE IMPORTANCE OF RESEARCH. THAT PUBLIC CONFIDENCE AND LEVEL OF EXPECTATION HAS DEVELOPED BECAUSE GREAT PROGRESS IN EXPANDING THE BORDERS OF FUNDAMENTAL KNOWLEDGE HAS MADE IT POSSIBLE TO PROCEED TO THE DEVELOPMENT OF POWERFUL MEASURES FOR THE PREVENTION AND TREATMENT OF DISEASES. BUT THE BASE OF KNOWLEDGE MUST COME FIRST, AND IT IS FOR THIS REASON THAT THE NIH CONTINUES ITS POLICY OF COMMITTING A LARGE SHARE OF ITS RESOURCES TO BASIC STUDIES.

BECAUSE PUBLIC AND PRIVATE FUNDS FOR RESEARCH ARE NOT UNLIMITED, IT IS INCUMBENT ON ALL OF US TO ASSURE THAT SUPPORT IS GIVEN TO WORK OF THE HIGHEST QUALITY. IN A RECENT SPEECH ON FEDERAL RESEARCH AND DEVELOPMENT POLICY, THE PRESIDENT'S SCIENCE ADVISOR, GEORGE KEYWORTH, COMMENTING ON MAKING BETTER USE OF OUR NATION'S RESEARCH RESOURCES, STATED THAT "GOOD INTENTIONS AND KEEPING BUSY DO NOT COUNT: RESULTS DO." "FOR THAT REASON," HE SAID, "OUR FIRST PRIORITY NOW IS TO PERMIT THE BEST RESEARCH TO BE MORE FULLY SUPPORTED SO THAT ITS INFLUENCE CAN BE EXTENDED. THIS IS THE TIME TO DO A JOB WITH THE BEST TOOLS WE HAVE, NOT A TIME TO DISSIPATE OUR RESOURCES BY PARCELING THEM OUT IN RESPONSE TO POPULAR DEMAND."

IN CARRYING OUT ITS MISSION, THE NIH IS NOT ONLY DEPENDENT UPON THE SCIENTIFIC COMMUNITY FOR THE INITIATION AND PROPOSAL OF RESEARCH SUBJECTS; IT ALSO DRAWS HEAVILY UPON THE NATION'S SCIENTIFIC COMMUNITY FOR THE EXPERTISE NEEDED IN MAKING THE CRITICAL JUDGMENTS AMONG COMPETING PROPOSALS.

PEER REVIEW IS AT THE VERY HEART OF THE NIH SYSTEM. WHILE I THINK IT IS LIKELY THAT MANY OF YOU HAVE HAD FIRSTHAND EXPERIENCE IN PREPARING AND SUBMITTING RESEARCH PROPOSALS AND IN CARRYING OUT RESEARCH FUNDED BY THE NIH, I WILL TAKE A MOMENT TO DESCRIBE THE OPERATION OF THE GRANTS REVIEW PROCESS.

WITH ONLY MINIMAL RESTRICTIONS, ANY INVESTIGATOR MAY APPLY FOR A RESEARCH PROJECT GRANT TO CARRY OUT SPECIFIED RESEARCH THAT IS RELATED TO THE OVERALL MISSION OF THE NIH. SOME FIFTEEN TO TWENTY THOUSAND RESEARCH GRANT APPLICATIONS ARE RECEIVED AND REVIEWED BY THE NIH EACH YEAR. IT HAS NEVER BEEN POSSIBLE FOR THE AGENCY TO FUND ALL GRANTS CONSIDERED WORTHY OF SUPPORT. AND THUS, FOR MORE THAN THIRTY YEARS, WE HAVE EMPLOYED THE PEER REVIEW SYSTEM TO ASSIST US IN MAKING THE CRUCIALLY IMPORTANT CHOICES AMONG GRANT APPLICATIONS. IN THIS PROCESS, WE RELY ALMOST EXCLUSIVELY ON MEMBERS OF THE NONFEDERAL SCIENTIFIC COMMUNITY. INVESTIGATORS IN THE MANY DISCIPLINES OF BIOMEDICAL SCIENCE ARE

APPOINTED TO INITIAL REVIEW COMMITTEES CALLED STUDY SECTIONS. THE STUDY SECTIONS ARE ORGANIZED ALONG TRADITIONAL DISCIPLINARY LINES; FOR EXAMPLE, HEMATOLOGY, CELL BIOLOGY, PHARMACOLOGY, ETC. SIXTY-FOUR COMMITTEES OF THIS TYPE MEET THREE TIMES EACH YEAR TO REVIEW GRANT APPLICATIONS ASSIGNED TO THEM. MEMBERS OF THE STUDY SECTIONS ARE CAREFULLY SELECTED ON THE BASIS OF THEIR OWN SCIENTIFIC PERFORMANCE AND ARE APPOINTED FOR FOUR-YEAR TERMS.

THE STUDY SECTIONS ASSESS THE SCIENTIFIC MERIT AND TECHNICAL FEASIBILITY OF GRANT APPLICATIONS AND ASSIGN TO EACH A RATING OR A PRIORITY SCORE. IN LATER CONSIDERATIONS, THAT SCORE BECOMES THE SINGLE MOST IMPORTANT FACTOR WHEN THE FINAL DECISION IS MADE TO FUND OR NOT TO FUND.

FOLLOWING REVIEW BY THE STUDY SECTIONS, THE GRANTS ARE THEN ASSIGNED FOR CONSIDERATION BY ONE OF THE ELEVEN INSTITUTES OF THE NATIONAL INSTITUTES OF HEALTH.

AT THE INSTITUTE, A SECOND REVIEW IS CONDUCTED BY THE NATIONAL ADVISORY COUNCIL OF THE PROSPECTIVE FUNDING INSTITUTE. THE NATIONAL ADVISORY COUNCILS INCLUDE IN THEIR MEMBERSHIP NOT ONLY SCIENTISTS BUT PUBLIC MEMBERS AS WELL.

IN THE COUNCILS, ADDITIONAL JUDGMENTS ARE MADE ON THE BASIS OF THE PROGRAM CONCERNS OF THE INSTITUTE. BY LAW, NO GRANT MAY BE AWARDED THAT HAS NOT BEEN RECOMMENDED FOR AWARD BY THE NATIONAL ADVISORY COUNCIL OF THE FUNDING INSTITUTE.

CURRENTLY, MANY STRONG, POTENTIALLY PRODUCTIVE, AND VALUABLE RESEARCH PROJECTS CANNOT BE FUNDED, AND EXCELLENT ESTABLISHED INVESTIGATORS AS WELL AS WELL-QUALIFIED NEWCOMERS ARE BEING DENIED SUPPORT BECAUSE OF THE STRINGENCY OF THE BUDGET. IT IS ONLY NATURAL, AT SUCH A TIME, THAT THE MECHANISM BY WHICH JUDGMENTS ARE MADE WOULD COME UNDER EXTERNAL PRESSURE. SOME SCIENTISTS HAVE ATTACKED THE FUNDAMENTAL INTEGRITY AND EQUITY OF THE PEER REVIEW SYSTEM.

IT IS A HUMAN SYSTEM AND NO ONE WOULD CONTEND THAT ITS JUDGMENTS ARE FLAWLESS. YET IT HAS OPERATED WITH VERY LITTLE CRITICISM FOR 30 YEARS AND WE CONTINUE TO HAVE THE STRONGEST CONFIDENCE IN ITS OVERALL PERFORMANCE.

THERE ALWAYS HAS BEEN A CUTOFF POINT BELOW WHICH GRANTS COULD NOT BE PAID DUE TO LIMITATION OF FUNDS. HOWEVER, THE DIFFERENCES IN QUALITY OF APPLICATIONS AT THE MARGIN ARE QUITE SMALL WHEN WE ARE ABLE TO PAY ONLY ONE-THIRD OF QUALIFIED APPLICATIONS AS COMPARED WITH THE DIFFERENCES WHEN WE COULD FUND ONE-HALF OR MORE OF THE WORTHY PROPOSALS. THE JUDGMENTS ARE MUCH MORE DIFFICULT AND UNREST IN THE EXTRAMURAL COMMUNITY IS CORRESPONDINGLY HIGHER. THE ONLY WAY TO AVOID THE PROBLEM ALTOGETHER IS TO BE ABLE TO PAY ALL APPROVED GRANTS, AND

THIS UTOPIAN DAY IS UNLIKELY EVER TO ARRIVE. APPLICANTS WHOSE PRIORITY SCORES FALL OUTSIDE THE PAY LINE ARE PROVIDED INFORMATION ON THE SHORTCOMINGS OF THEIR APPLICATIONS AND HAVE THE OPTION OF REWRITING THEIR MATERIAL AND RESUBMITTING. LAST YEAR, ONE-FOURTH OF ALL APPLICATIONS WERE RESUBMISSIONS, A CATEGORY OF APPLICATIONS THAT HAS DOUBLED IN SIZE IN THE PAST THREE TO FIVE YEARS.

FOR THOSE OF US WHO IN ONE WAY OR ANOTHER HAVE HAD CONTACT WITH THE NIH OVER A PERIOD OF TIME, THESE SIGNS OF STRESS SHOULD COME AS NO SURPRISE. THE AGENCY WENT THROUGH A SPECTACULAR PERIOD OF GROWTH IN THE MID-FIFTIES AND EARLY SIXTIES. BUT, OF COURSE, IT WOULD HAVE BEEN UNREALISTIC TO EXPECT THAT RATE OF GROWTH TO CONTINUE INDEFINITELY.

(SLIDE 3) DURING THE PAST DECADE, THE GROWTH IN SUPPORT HAS BEEN MORE APPARENT THAN REAL--THE 1979 APPROPRIATION OF $3.2 BILLION REPRESENTS AN ALL-TIME HIGH IN CONSTANT DOLLARS, BUT WAS WORTH ONLY $1.92 BILLION IN 1972 DOLLARS. BETWEEN 1979 AND 1982, THE CONSTANT DOLLAR LEVEL FELL BY 12 PERCENT. A SLIGHT INCREASE TO THE 1983 LEVEL OF $1.77 BILLION INDICATES THAT FOR THE PRESENT AT LEAST THE DECLINE IN PURCHASING POWER HAS LEVELED OFF.

BETWEEN 1973 AND 1983, AN INCREASE OF ABOUT FIVE PERCENT WAS MORE THAN MATCHED BY THE INCREASE IN INDIRECT COSTS. THEREFORE, THE DOLLARS AVAILABLE FOR THE DIRECT COSTS OF RESEARCH HAVE ACTUALLY DECLINED SLIGHTLY DURING A DECADE WHEN THE NUMBER OF CAPABLE AND MATURING SCIENTISTS HAS MUCH INCREASED AND SCIENTIFIC OPPORTUNITY IS GREATER THAN EVER BEFORE.

PRESIDENT REAGAN'S BUDGET REQUEST FOR 1984 IS NOW UNDER CONSIDERATION BY THE CONGRESS. THE 1984 REQUEST FOR NIH IS $4.077 BILLION, AN INCREASE OF 73 MILLION OR 1.8 PERCENT OVER THE 1983 LEVEL.

I. L. STONE HAS REVISED McLUHAN'S FAMILIAR DICTUM TO MAKE IT READ, "IN GOVERNMENT THE BUDGET IS THE MESSAGE." THE ADMINISTRATION'S 1984 BUDGET PROPOSAL REQUESTS SUBSTANTIAL INCREASES FOR DEFENSE R&D AND FOR PHYSICAL SCIENCES. BUT AS YOU KNOW, RECENT ADMINISTRATIONS HAVE GENERALLY REQUESTED ONLY MODEST INCREASES FOR NIH, SINCE CONGRESS HAS CONSISTENTLY BEEN DISPOSED TO APPROPRIATE FUNDS IN EXCESS OF THE REQUEST. IN 1983 FOR EXAMPLE, CONGRESS PROVIDED 9.9 PERCENT FOR NIH, 6 PERCENT MORE THAN THE ADMINISTRATION'S BUDGET.

A FEW MONTHS AGO IN EARLY FEBRUARY OF THIS YEAR, I WAS PRIVILEGED TO VISIT BAYLOR COLLEGE OF MEDICINE AND PRESENT THE 11TH "SCIENCE AND SOCIETY" LECTURE IN THE DISTINGUISHED SERIES HONORING VERNA AND MARRS McLAIN. MY SUBJECT WAS "SUPPORT OF THE BIOSCIENCES AND THE ZERO-SUM GAME." AT THAT TIME, THE PRESIDENT

HAD JUST ANNOUNCED HIS 1984 BUDGET REQUESTS FOR ALL GOVERNMENT AGENCIES. AS I HAVE MENTIONED EARLIER, THE TOTAL PROPOSED FOR NIH WAS $4.077 BILLION. AS USUAL, THE NIH PREPARED DETAILED INFORMATION ON HOW THE TOTAL WOULD BE DISTRIBUTED AMONG THE CONSTITUENT UNITS AND FUNDING MECHANISMS. IT WAS THEN OUR ESTIMATE THAT THE NUMBER OF NEW AND COMPETING GRANTS THAT COULD BE AWARDED UNDER THE BUDGET WOULD BE 3,676 -- SUBSTANTIALLY FEWER THAN THE NOMINAL STABILIZATION LEVEL OF 5,000. IN THE HECTIC LAST FEW DAYS BEFORE THE BUDGET WAS SUBMITTED, THE NIH PLAN FOR USE OF THE FUNDS WAS TENTATIVELY APPROVED AND FILED WITH THE APPROPRIATIONS COMMITTEE AS A DRAFT. ACCOMPANYING THE DRAFT WAS A LETTER FROM SECRETARY SCHWEIKER, SIGNED ONLY TWO DAYS BEFORE HIS RESIGNATION BECAME EFFECTIVE, FEBRUARY 4. IN THE LETTER, SECRETARY SCHWEIKER ADVISED THAT IT IS THE ADMINISTRATION'S POLICY FOR 1984 THAT THE NIH FUND 5,000 NEW AND COMPETING RESEARCH GRANTS.

HE NOTED THAT DISCUSSIONS WERE CURRENTLY UNDER WAY BETWEEN THE DEPARTMENT AND THE OFFICE OF MANAGEMENT AND BUDGET ON THE RESOURCE ADJUSTMENTS NECESSARY TO ACHIEVE THE DESIRED NUMBER OF GRANTS. SUBSEQUENTLY, THE FINAL DECISIONS ON THE ADJUSTMENTS WERE MADE JUST BEFORE WE WERE REQUIRED TO GO BEFORE THE HOUSE APPROPRIATIONS COMMITTEE IN EARLY APRIL TO PRESENT A DETAILED JUSTIFICATION OF THE REQUESTS. IT WAS THE OMB'S DECISION THAT NO ADDITIONS WOULD BE MADE TO THE OVERALL ORIGINAL BUDGET ESTIMATES FOR THE NIH. THIS MEANT THAT ADJUSTMENTS WOULD HAVE TO BE MADE INTERNALLY IN THE ALLOCATIONS THAT HAD BEEN PROPOSED FOR OTHER PROGRAM MECHANISMS TO PERMIT THE AWARD DURING 1984 OF THE TARGETED NUMBER OF NEW AND COMPETING GRANTS. I MENTION THIS SITUATION BECAUSE IT PROVIDES A CLEAR ILLUSTRATION OF THE TRANSLATION OF A POLICY DECISION INTO THE LINE ITEMS OF A BUDGET.

IT WAS DURING THE BUDGET DEVELOPMENT PERIOD THREE YEARS AGO THAT THE DECISION WAS MADE THAT THE NIH SHOULD ENDEAVOR TO "STABILIZE" ITS ANNUAL ALLOWANCE FOR NEW AND COMPETING GRANTS. TO DAMPEN THE ROLLER COASTER FLUCTUATIONS IN THE NUMBER OF NEW GRANTS FROM YEAR TO YEAR, A POLICY DECISION WAS MADE TO ATTEMPT TO STABILIZE SUCH GRANTS AT APPROXIMATELY 5,000 EACH YEAR. THIS STABILIZATION EFFORT HAS CONTINUED TO BE A DOMINANT FACTOR IN OUR BUDGET DEVELOPMENT, CERTAINLY IN THE BUDGET NOW BEFORE THE CONGRESS.

THE STABILIZATION POLICY WAS DESIGNED AS A POWERFUL STATEMENT TO THE EXTRAMURAL COMMUNITY, SAYING THAT THE NIH IS DOING ITS UTMOST CONSISTENT WITH PROGRAM BALANCE AND CONGRESSIONAL MANDATES AND DIRECTIVES TO ASSURE THAT THE BEST RESEARCH WILL BE ADEQUATELY FUNDED; THAT YOUNG SCIENTISTS WILL HAVE OPPORTUNITIES IN RESEARCH; AND THAT WE WILL PROTECT THEIR ENTRY INTO THE RESEARCH ENTERPRISE, BECAUSE THE VITALITY AND SUCCESS OF THE RESEARCH ENDEAVOR DEPENDS ON THEM.

LET US FOCUS FOR A MOMENT ON RESEARCH MANPOWER AND TRAINING. WE BELIEVE THAT TO ASSURE THE CONTINUED SUCCESS OF RESEARCH ACTIVITY, AN ACTIVE RESEARCH MANPOWER DEVELOPMENT PROGRAM MUST BE SUSTAINED FOR SELECT INDIVIDUALS AT ALL STAGES OF INTELLECTUAL AND PROFESSIONAL DEVELOPMENT. THIS UNDERLYING PHILOSOPHY WAS SUCCINCTLY STATED IN THE PREAMBLE TO THE CONGRESSIONAL ACT UNDER WHICH MANY OF OUR TRAINING PROGRAMS ARE CARRIED OUT. THE CONGRESS DECLARED THAT (1) THE SUCCESS AND CONTINUED VIABILITY OF THE FEDERAL BIOMEDICAL AND BEHAVIORAL RESEARCH EFFORT DEPENDS ON THE AVAILABILITY OF EXCELLENT SCIENTISTS AND A NETWORK OF INSTITUTIONS OF EXCELLENCE CAPABLE OF PRODUCING SUPERIOR RESEARCH PERSONNEL; (2) DIRECT SUPPORT OF THE TRAINING OF SCIENTISTS FOR CAREERS IN BIOMEDICAL AND BEHAVIORAL RESEARCH IS AN APPROPRIATE AND NECESSARY ROLE FOR THE FEDERAL GOVERNMENT; AND (3) GRADUATE RESEARCH ASSISTANCE PROGRAMS SHOULD BE THE KEY ELEMENT IN THE TRAINING PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH.

FROM OUR POINT OF VIEW, THE TRAINING AND RESEARCH PROGRAMS ARE SO CLOSELY INTERWOVEN AS TO BE PRACTICALLY INDIVISIBLE. AS A MATTER OF FACT, ALTHOUGH IN OUR DICUSSIONS OF THE STABILIZATION INITIATIVE WE USUALLY MENTION ONLY THE NEED FOR 5,000 NEW AND COMPETING GRANTS, OUR STABILIZATION POLICY ALSO EXTENDS TO THE GOAL OF 10,000 TRAINEES IN ACADEMIC INSTITUTIONS THROUGHOUT THE NATION.

THIS BOND BETWEEN TRAINING AND RESEARCH WAS ADDRESSED IN DR. KEYWORTH'S STATEMENT ON FEDERAL POLICY TO WHICH I REFERRED EARLIER IN THIS DISCUSSION. HE NOTED THAT "AS A GROUP, AMERICAN RESEARCH UNIVERSITIES ARE THE BEST IN THE WORLD, BOTH IN TERMS OF PRODUCING THE NEW KNOWLEDGE THAT STIMULATES TECHNOLOGY AND IN TERMS OF PRODUCING THE PEOPLE WHO DRIVE THE INNOVATIVE PROCESS IN SOCIETY. THAT UNIQUE DUAL FUNCTION," HE SAYS, "EXPLAINS OUR TREMENDOUS EMPHASIS ON UNIVERSITY RESEARCH. NO OTHER RESEARCH INSTITUTIONS--FEDERAL LABORATORIES, NONPROFIT ORGANIZATIONS, OR INDUSTRIAL LABORATORIES--GIVE SO MUCH IN RETURN ON INVESTMENT IN THE LONG TERM. NO OTHER INSTITUTIONS PRODUCE BOTH KNOWLEDGE AND PEOPLE."

THE INTENSE COMPETITION FOR RESEARCH SUPPORT HAS INCREASINGLY TAKEN ITS TOLL OF THE AMATEUR OR UNDERTRAINED INVESTIGATOR. THE PROFESSIONALIZATION OF RESEARCH ACTIVITY HAS PROGRESSIVELY SELECTED AGAINST THE M.D. SCIENTIST WHO FIFTEEN YEARS AGO HAD A MUCH BETTER PROSPECT OF SUCCESS IN RESEARCH APPLICATIONS THAN THE PH.D. APPLICANT. SINCE 1974, APPLICANTS HAVING BOTH THE M.D. AND PH.D. DEGREES HAVE ENJOYED THE HIGHEST SUCCESS RATE, FOLLOWED BY THOSE WITH PH.D.'S. THE M.D. SCIENTIST IS COMPETING STEADILY LESS WELL. (SLIDE 4)

THE NATIONAL ACADEMY OF SCIENCES CONDUCTS A CONTINUING STUDY OF THE NATIONAL NEEDS FOR BIOMEDICAL AND BEHAVIORAL RESEARCH PERSONNEL. THE FINDINGS OF THE STUDY ARE USED BY THE NIH IN PLANNING FOR ITS RESEARCH TRAINING PROGRAM.

A MAJOR CONCERN OF THE ACADEMY AND ALSO OF THE NIH HAS BEEN A DECREASE IN THE NUMBER OF PHYSICIANS WHO ARE SEEKING RESEARCH TRAINING. THE ACADEMY RECOMMENDED THAT AT LEAST 2,800 INDIVIDUALS HOLDING THE M.D. OR EQUIVALENT DEGREE BE SUPPORTED UNDER THE ESTABLISHED RESEARCH TRAINING PROGRAM EVERY YEAR. THAT GOAL HAS NOT BEEN REACHED. AS A MATTER OF FACT, THERE HAS BEEN A CONSIDERABLE DECLINE IN THE NUMBERS OF PROFESSIONAL DEGREE HOLDERS UNDERTAKING RESEARCH TRAINING. (SLIDES 5 AND 6) WHILE THE ABSOLUTE NUMBER OF CLINICAL POSTDOCTORAL FELLOWS HAS LEVELED OFF TO A RELATIVELY CONSTANT NUMBER IN THE RANGE OF 1,900 PER YEAR SINCE 1976, IT FALLS FAR SHORT OF MEETING THE ACADEMY'S RECOMMENDATIONS.

THE APPLICATION OF SCIENTIFIC ADVANCES TO MAINTAIN GOOD HEALTH AND TO PREVENT AND TREAT DISEASE IS ULTIMATELY THE RESPONSIBILITY OF THE PHYSICIAN. THE TRAINED CLINICAL INVESTIGATOR IS THE CRITICAL LINK BETWEEN THE LABORATORY AND THE HEALTH CARE PROVIDER. IN THE FACE OF THE EXPLOSIVE GROWTH OF BASIC KNOWLEDGE IN THE BIOMEDICAL SCIENCES WHICH HAS OPENED UP VAST OPPORTUNITIES FOR CLINICAL RESEARCH, THE SHORTFALL IN TRAINING OF CLINICAL INVESTIGATORS ASSUMES ADDITIONAL SIGNIFICANCE.

AMONG THE REASONS CITED FOR THE DECLINING INTEREST OF PHYSICIANS IN CLINICAL RESEARCH ARE THE FOLLOWING:

- EXTRAORDINARY INCOMES ARE AVAILABLE IN PRACTICE, ESPECIALLY IN THE PROCEDURE-ORIENTED SUBSPECIALITIES.

- THE DEBT LOAD OF MEDICAL STUDENTS HAS GROWN ENORMOUSLY. WHILE THE AVERAGE IS ABOUT $19,000, DEBTS AS HIGH AS $30,000 UPON GRADUATION ARE NOT UNUSUAL.

- THE NIH TRAINING STIPEND PAYS ON THE AVERAGE $6,000 PER YEAR LESS THAN DOES CLINICAL SPECIALTY TRAINING.

- THE AVERAGE MEDICAL SCHOOL CURRICULUM CONTAINS LITTLE OR NO OPPORTUNITY FOR LABORATORY EXPERIENCE.

- SPECIALTY TRAINING PROGRAMS HAVE LENGTHENED AND ARE QUITE RIGID WITH RESPECT TO INCLUSION OF RESEARCH TRAINING.

- o THE GROWING SOPHISTICATION OF SCIENCE AND ITS PROFESSIONALIZATION IN CLINICAL DEPARTMENTS REQUIRES THAT THE RECIPIENTS OF EVEN THE FINEST MEDICAL EDUCATION AND RESIDENCY TRAINING SPEND A SUBSTANTIAL AMOUNT OF ADDITIONAL TIME, AS LONG AS THREE YEARS, OBTAINING THE NECESSARY SKILLS TO BE SUCCESSFUL IN RESEARCH.

IN THE FACE OF THESE NEGATIVE FACTORS AND PARTLY TO COUNTER THEM, THE NIH HAS DEVELOPED SEVERAL PROGRAMS IN ADDITION TO ITS REGULAR RESEARCH TRAINING GRANTS THAT ARE DESIGNED TO ACQUAINT THE PHYSICIAN IN TRAINING WITH THE EXCITEMENT AND POSSIBILITIES OF BIOMEDICAL RESEARCH:

1. BECAUSE MEDICAL CURRICULA TODAY HAVE ELIMINATED MANY OF THE LABORATORY EXERCISES WHICH ONCE INTRODUCED STUDENTS TO RESEARCH TECHNIQUES, THE NIH HAS INITIATED A PROGRAM OF SHORT-TERM TRAINING IN HEALTH PROFESSIONAL SCHOOLS TO EXPOSE STUDENTS EARLY IN THEIR PROFESSIONAL STUDIES TO OPPORTUNITIES IN RESEARCH. THE PROGRAM NOW SUPPORTS MORE THAN 1,100 STUDENTS A YEAR DURING VACATION OR OFF-QUARTER PERIODS IN APPROXIMATELY 70 SCHOOLS OF MEDICINE, DENTISTRY, PHARMACY, AND VETERINARY MEDICINE.

2. A SECOND PROGRAM PROVIDING AN EARLY RESEARCH EXPERIENCE IS A SUMMER FELLOWSHIP AT THE NIH OFFERED TO OUTSTANDING MEDICAL STUDENTS THROUGHOUT THE COUNTRY. LAST YEAR, 52 MEDICAL AND DENTAL STUDENT FELLOWS SELECTED FROM VARIOUS INSTITUTIONS CONDUCTED LABORATORY RESEARCH AND ATTENDED LECTURES AND SEMINARS AT NIH.

3. A THIRD INITIATIVE FOR ATTRACTING MEDICAL STUDENTS INTO RESEARCH IS ONE OFTEN CALLED THE "POST-SOPHOMORE FELLOWSHIP." IT IS OUR VIEW THAT A SHORT-TERM EXPOSURE TO RESEARCH, ALTHOUGH USEFUL AS AN INTRODUCTION, IS LESS EFFECTIVE THAN A LONGER INITIAL LABORATORY EXPERIENCE. ACCORDINGLY, THE NIH IN THE SUMMER OF 1982 RE-ESTABLISHED A PROGRAM FOR SUPPORT OF STUDENTS WHO INTERRUPT PROFESSIONAL EDUCATION FOR A FULL YEAR OF RESEARCH TRAINING.

4. THE NEWEST ADDITION TO THE CAREER DEVELOPMENT AWARD PROGRAM, CALLED THE CLINICIAN-SCIENTIST AWARD, WILL BE ANNOUNCED NEXT MONTH. THIS AWARD WILL BE SUPPORTED BY SEVERAL OF THE NIH INSTITUTES. IT IS DESIGNED TO PROVIDE FIVE YEARS OF PHASED SUPERVISED RESEARCH TRAINING. THE FIRST FEW YEARS OF RESEARCH TRAINING WILL BE OBTAINED IN A BASIC SCIENCE DEPARTMENT. THE AWARD WILL CARRY A SALARY EQUIVALENT TO THAT EARNED BY A MEMBER OF THE INSTITUTION'S HOUSE STAFF WITH EQUIVALENT EXPERIENCE AND WILL INCLUDE $10,000 FOR RESEARCH COSTS. THE SECOND PHASE UNDERTAKEN AT A MORE INDEPENDENT LEVEL WILL HAVE UP TO $20,000 AVAILABLE TO COVER RESEARCH COSTS. AT THE CONCLUSION OF THIS FIVE-YEAR PROGRAM,

A YOUNG PHYSICIAN-SCIENTIST SHOULD BE WELL PREPARED TO COMPETE FOR NIH RESEARCH GRANT SUPPORT.

5. IN ADDITION, WE ARE CONTINUING TO GIVE TOP PRIORITY TO THE M.D./PH.D OR MEDICAL SCIENTIST TRAINING PROGRAM.

IN THE BEGINNING OF THIS DISCUSSION OF FEDERAL POLICY, I REFERRED TO THE BROAD CHARTER GIVEN TO NIH THROUGH SECTION 301 OF THE PUBLIC HEALTH SERVICE ACT OF 1944. AT THIS TIME, THE CONGRESS IS CONSIDERING THE HEALTH RESEARCH EXTENSION ACT OF 1983 WHICH WOULD SUPERCEDE ALL EXISTING AUTHORITIES FOR NIH PROGRAMS REPLACING THE BROAD CHARTER WITH A COMBINATION OF ENUMERATED AUTHORITIES AND GENERAL PROVISIONS. ASSISTANT SECRETARY FOR HEALTH, YOUR FELLOW TEXAN, ED BRANDT, TESTIFIED ON THIS BILL IN LATE FEBRUARY STATING OUR POSITION THAT SUCH EXTENSIVE CHANGES IN THE LANGUAGE OF THE ACT WOULD DISRUPT THE ORDERLY MANAGEMENT AND OPERATING PROCEDURES OF NIH AS A WHOLE AND OF THE INDIVIDUAL INSTITUTES. HE STATED THAT "WE ALSO BELIEVE THE DEGREE OF DETAIL AND SPECIFICITY IN THE BILL WOULD CREATE ORGANIZATIONS AND PROCEDURES THAT ARE TOO RIGIDLY DEFINED AND, IN FACT, REPRESENTS AN ATTEMPT TO MICROMANAGE THE NIH."

THIS PROPOSED LEGISLATION CONSTITUTES A KIND OF CATALOG OF IMPORTANT ISSUES FACING THE NIH AND THE BIOMEDICAL RESEARCH COMMUNITY AT THIS TIME. IT FORMS A USEFUL FRAMEWORK FOR DISCUSSION OF MATTERS TO WHICH WE AS PARTNERS IN THE RESEARCH ENTERPRISE MUST GIVE OUR ATTENTION FOR THIS LEGISLATION WOULD BE HIGHLY DAMAGING TO NIH.

WE ARE INCREASINGLY CONCERNED ABOUT SUCH HIGHLY SPECIFIC LEGISLATION WHICH IN PART RESULTS FROM INCREASING COMPETITION AMONG SCIENTISTS AND LAY ADVOCATES OF SPECIFIC DISEASE RESEARCH PROGRAMS WHO SEEK TARGETED FUNDING OR SPECIFIC LEGISLATIVE PRIORITY.

OVER THE PAST TEN YEARS, THERE HAVE BEEN OVER 10 LEGISLATIVE PROPOSALS TO ESTABLISH NEW NIH INSTITUTES AND NUMEROUS PROPOSALS TO SET ASIDE FUNDS OR OTHERWISE TO PLACE SPECIAL EMPHASIS ON CERTAIN PROGRAMS RELATED TO SPECIFIC DISEASES OR SYSTEMS OF THE BODY. THE UNFORTUNATE CONSEQUENCE OF THESE MANDATES IS TO LIMIT INCREASINGLY THE ABILITY OF NIH TO SUPPORT A BROAD RANGE OF RESEARCH PROJECTS DIRECTED AT THE WHOLE SPECTRUM OF ACTIVITIES THAT ARE DESIGNED TO UNDERSTAND, PREVENT, AND TREAT DISEASE.

THE PROPOSED LEGISLATION WOULD REQUIRE SPECIFIC EARMARKS OF FUNDS OR SPECIAL EMPHASIS OR ACTIVITIES FOR:

- HEALTH PROMOTION AND DISEASE PREVENTION CENTERS
- CANCER CENTERS
- KIDNEY AND UROLOGIC DISEASES RESEARCH CENTERS
- RESEARCH IN SPINAL CORD REGENERATION
- OPERATION OF THE NATIONAL CENTER FOR HEALTH CARE TECHNOLOGY
- SICKLE CELL DISEASE CENTERS
- PERTUSSIS VACCINE STUDY
- STUDY OF PERSONNEL FOR HEALTH NEEDS OF THE ELDERLY
- STUDY OF COMMERCIAL USE OF BIOMEDICAL RESEARCH RESULTS
- INTERAGENCY COMMITTEE ON LEARNING DISABILITIES
- RESEARCH INTO DIET THERAPY IN THE TREATMENT OF END STAGE RENAL DISEASE
- RESEARCH IN THE RELATIONSHIP BETWEEN DIET AND CANCER
- RESEARCH IN DEVELOPING RESEARCH METHODS THAT REDUCE THE USE OF ANIMALS OR MINIMIZE ANIMAL PAIN
- MENTAL RETARDATION CENTERS
- NATIONAL COMMISSION ON ORPHAN DISEASES

THE BILL CONTAINS MANY OTHER SPECIFIC TECHNICAL AND ADMINISTRATIVE DIRECTIONS. IT APPEARS THAT VIRTUALLY EVERY REPRESENTATION OF A SPECIAL INTEREST GROUP HAS GIVEN RISE TO A RESTRICTIVE AMENDMENT AFFECTING NIH. WE CONTINUE TO OPPOSE THE "WAXMAN BILL" AND FAVOR SIMPLE REAUTHORIZATION OF THOSE NIH CHARTERS THAT WILL EXPIRE.

NIH'S MISSION IS CLEAR AND UNAMBIGUOUS--TO IMPROVE THE HEALTH OF THE NATION THROUGH THE CONDUCT AND SUPPORT OF RESEARCH AND, IN PARTICULAR, THE GENERATION OF KNOWLEDGE. NIH DOES NOT PROVIDE HEALTH SERVICES, AND ITS REGULATORY RESPONSIBILIES ARE LIMITED TO SETTING STANDARDS FOR USE OF HUMAN AND ANIMAL SUBJECTS IN RESEARCH. THE CURRENT ORGANIZATION OF NIH WHICH HAS EVOLVED OVER A PERIOD OF 50 YEARS IS SUFFICIENTLY BROAD TO ACCOMMODATE CHANGES IN SCIENTIFIC DIRECTION AND SCOPE AND TO COLLABORATE WITH OTHER PHS AGENCIES IN TRANSFERRING KNOWLEDGE INTO THE HEALTH CARE SYSTEM.

WE ARE CONCERNED, FOR EXAMPLE, ABOUT THE IMPACT ON THE RESEARCH PROGRAMS OF THE NIH OF PROPOSALS THAT WOULD REQUIRE THE ESTABLISHMENT OF STATUTORY PREVENTIVE-RELATED STAFF OFFICES IN EACH INSTITUTE AND CREATE 25 PREVENTION RESEARCH AND DEMONSTRATION CENTERS.

PREVENTION OF DISEASE AND DISABILITY IS THE ULTIMATE GOAL OF ALL NIH RESEARCH PROGRAMS, BUT RESEARCH INTO PREVENTION MUST REST ON A FIRM SCIENTIFIC BASE AND BE CLOSELY LINKED WITH OTHER RESEARCH EFFORTS. WHERE SUCH A BASE EXISTS, SERIOUS ATTENTION IS BEING GIVEN TO RESEARCH INTO PREVENTION OF DISEASE. FOR SOME INSTITUTES AND IN SOME DISEASE AREAS, PREVENTION RESEARCH IS MORE THAN FULLY WARRANTED AND, IN FACT, IS BEING CARRIED OUT. IN OTHERS THE TIME IS NOT RIPE AND THE PROPOSED ORGANIZATIONAL STRUCTURE IS INAPPROPRIATE. WHAT IS NEEDED IS THE FLEXIBILITY THAT NOW EXISTS FOR THE OPTIMUM DEPLOYMENT OF SCIENTIFIC AND FINANCIAL RESOURCES.

I WILL MENTION ONE MORE AMENDMENT TO THE REAUTHORIZATION BILL BY WAY OF BRINGING UP A GENERAL PROBLEM ABOUT WHICH WE MUST ALL BE CONCERNED.

IN THE LAST YEAR OR SO, THERE HAS BEEN A MARKED UPSURGE IN ACTIVITY BY PUBLIC GROUPS ATTACKING THE USE OF ANIMALS IN RESEARCH. WE ARE SEEING FOR THE FIRST TIME JOINT EFFORTS BY VARIOUS ANIMAL RIGHTS GROUPS BRINGING TOGETHER THE MORE TRADITIONAL ORGANIZATIONS WITH THE MORE EXTREME ACTIVIST GROUPS.

THEIR PUBLIC RELATIONS AND EMOTIONAL MEDIA CAMPAIGNS HAVE BEEN CARRIED OUT SKILLFULLY AND SEEM LIKELY TO BE ON THE INCREASE. THE CONGRESS HAS BEEN BOMBARDED BY MAIL AND IN THE FACE OF SUCH CONSTITUENT PRESSURES, IT IS ALMOST INEVITABLE THAT LEGISLATION ON THE SUBJECT WILL EMERGE.

WE MUST MAKE THE PUBLIC AWARE OF THE CRITICAL IMPORTANCE OF ANIMAL RESEARCH TO IMPROVEMENTS IN HUMAN HEALTH CARE AND DISEASE PREVENTION. WE MUST ALSO DEMONSTRATE BY ACTION OUR CONCERN FOR THE ETHICAL AND HUMANE TREATMENT OF ANIMAL SUBJECTS OF RESEARCH. UNLESS WE CAN GET BOTH OF THESE MESSAGES ACROSS TO THE PUBLIC AND THE CONGRESS, I BELIEVE WE ARE LIKELY TO SEE A SERIES OF PROGRESSIVELY RESTRICTIVE LEGISLATIVE MEASURES GOVERNING THE USE OF ANIMALS.

IN CONCLUSION, I WOULD LIKE TO MENTION THREE ISSUES THAT ARE OF LONGER RANGE SIGNIFICANCE PERHAPS THAN THE CATALOG OF ISSUES UNDER DISCUSSION NOW IN THE CONGRESS. I INCLUDE ON THIS LONG RANGE LIST AS FOREMOST THE NEED TO ASSURE ADEQUATE LEVELS OF SUPPORT FOR THE RESEARCH ENTERPRISE. CURRENTLY, OUR AWARD RATE IS 33 PERCENT OF APPROVED APPLICATIONS. WE BELIEVE AN OPTIMAL LEVEL FOR PROGRESS WOULD BE 45 TO 50 PERCENT. IN THE CONTEXT OF THE FEDERAL BUDGET, THE SUMS NEEDED ARE NOT LARGE. TO ACHIEVE THIS GOAL, WE WOULD NEED AN

ADDITIONAL $300 TO $400 MILLION PER YEAR FOR THREE YEARS AND THEREAFTER AN ANNUAL BUDGET OF $5 BILLION ADJUSTED FOR INFLATION.

A SIMILAR PROBLEM EXISTS IN REPLACING OR PURCHASING THE INCREASINGLY SOPHISTICATED RESEARCH INSTRUMENTATION OUR LABORATORIES NOW REQUIRE. IT IS ESTIMATED THAT $20 MILLION A YEAR FOR FIVE YEARS IS NEEDED FOR THE ACQUISITION OF LARGE-SCALE SHARED INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE BY RESEARCH GRANTS OF SMALLER INSTRUMENTS.

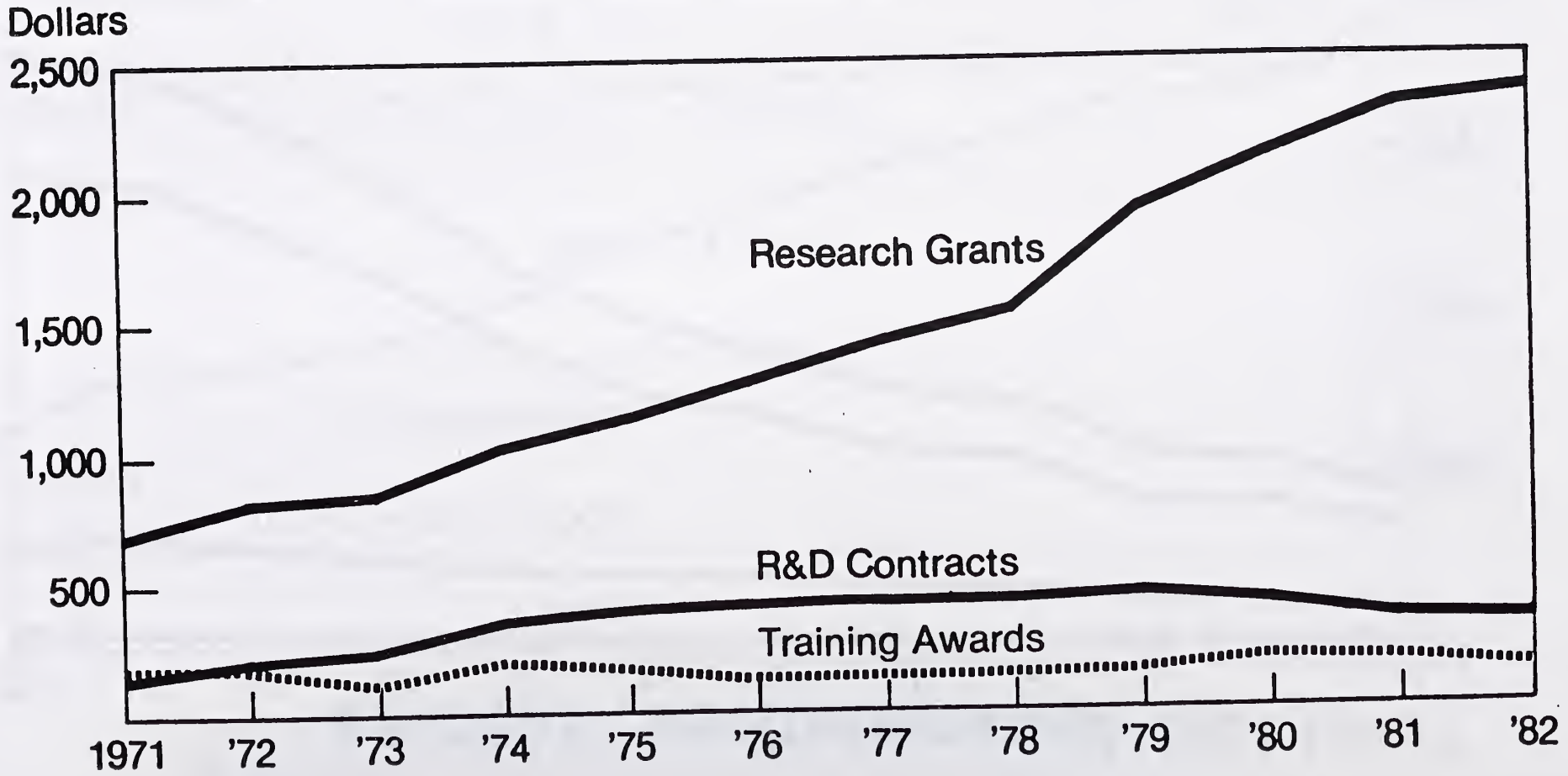
FINALLY, EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND MORE RECENTLY BY THE EYE INSTITUTE, NIH STOPPED SUPPORTING FACILITIES AFTER 1969. WE NEED TO HELP MODERNIZE AND TO CONSTRUCT NEW LABORATORIES.

I WANT TO EMPHASIZE THAT IT IS NOT POSSIBLE TO ACCOMPLISH THESE GOALS IN THE IMMEDIATE FUTURE. GIVEN THE CURRENT STATE OF THE ECONOMY, I BELIEVE NIH HAS FARED WELL. OUR BUDGET REPRESENTS A STRONG COMMITMENT BY THE ADMINISTRATION AND THE CONGRESS TO BIOMEDICAL RESEARCH. BUT I ALSO BELIEVE THAT AS THE ECONOMY IMPROVES, IT IS IMPERATIVE TO INCREASE THAT LEVEL OF SUPPORT.

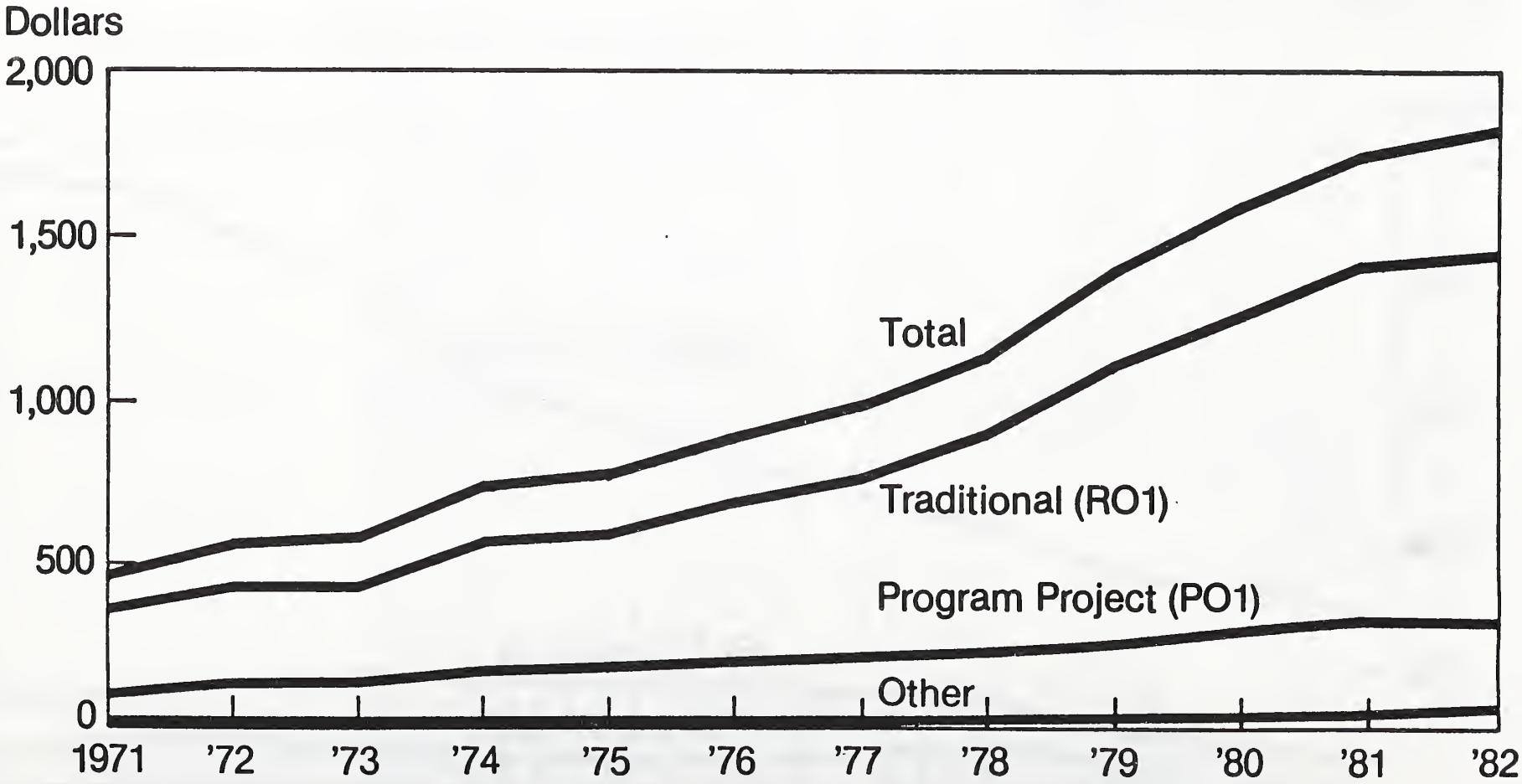
OUR PAST HISTORY OF COOPERATION WITH THE NONFEDERAL SCIENTIFIC COMMUNITY IN THE EVOLUTION OF OUR NATION'S GREAT BIOMEDICAL RESEARCH ENTERPRISE GIVES ME CONFIDENCE IN OUR ABILITY TO SOLVE CURRENT PROBLEMS THROUGH WORKING TOGETHER. WHILE WE ALL ENCOURAGE THE INTENSE COMPETITION THAT DRIVES SCIENTIFIC DISCOVERY, WE SHOULD VIEW OURSELVES AS COLLABORATORS IN THE OPERATION OF THE SYSTEM THAT SUPPORTS THE RESEARCH EFFORTS. WE ARE VITALLY CONCERNED FOR THE HEALTH AND STABILITY OF THE INSTITUTIONS IN WHICH SO MUCH OF THE ESSENTIAL RESEARCH IS CONDUCTED, JUST AS THEY ARE FOR THE SUCCESS OF THE NIH. THE ENLIGHTENED FEDERAL POLICY ON BIOMEDICAL RESEARCH IN THIS COUNTRY HAS BEEN UNUSUALLY SUCCESSFUL. GOVERNMENT AND THE SCIENTIFIC COMMUNITY HAVE FORMED A STRONG AND HEALTHY PARTNERSHIP BASED ON LONG-STANDING PRINCIPLES OF COOPERATION IN THE CAUSE OF SCIENCE, AND THE STRENGTH OF THIS PARTNERSHIP WILL SERVE US WELL IN ARRIVING AT MUTUALLY SATISFACTORY AND PRODUCTIVE SOLUTIONS TO THE PROBLEMS WE BOTH FACE. WE SHARE OBJECTIVES OF THE HIGHEST MERIT; NAMELY, THE CONQUEST OF DISEASE AND BETTER HEALTH FOR ALL.

(1)

NIH Extramural Programs, 1971-82
(Millions of Dollars)

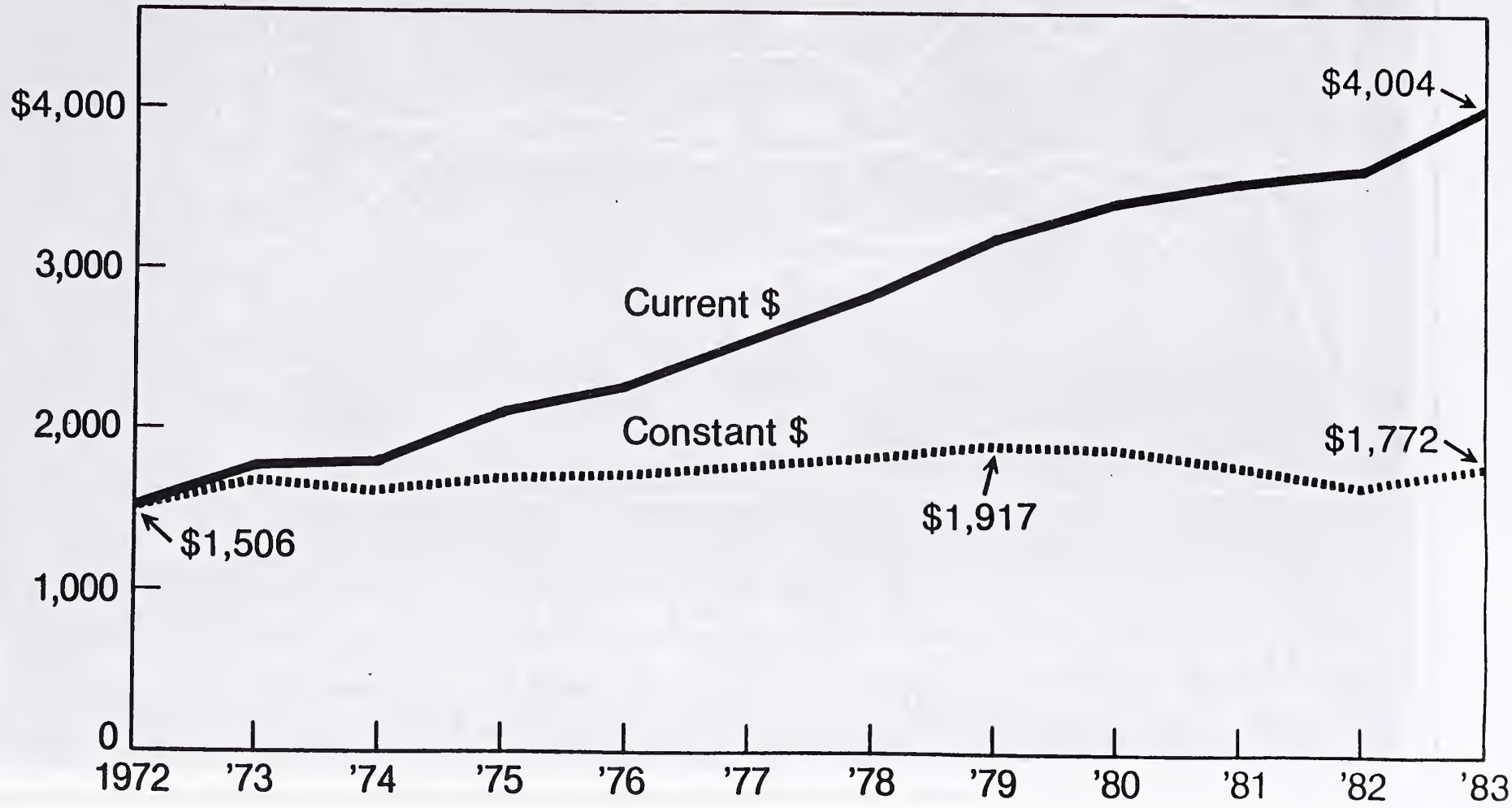


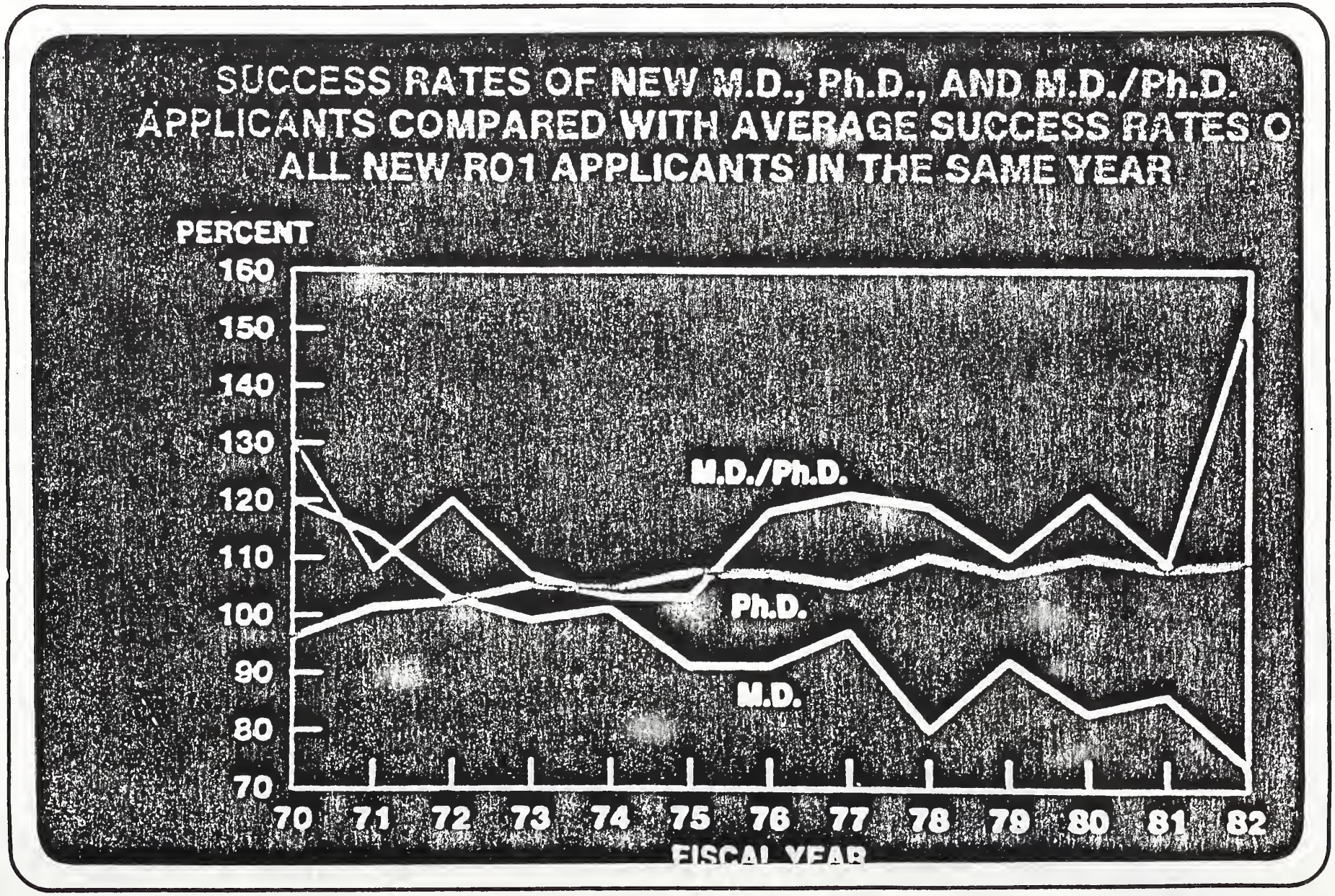
Research Project Grants, 1971-82
(Millions of Dollars)



(3)

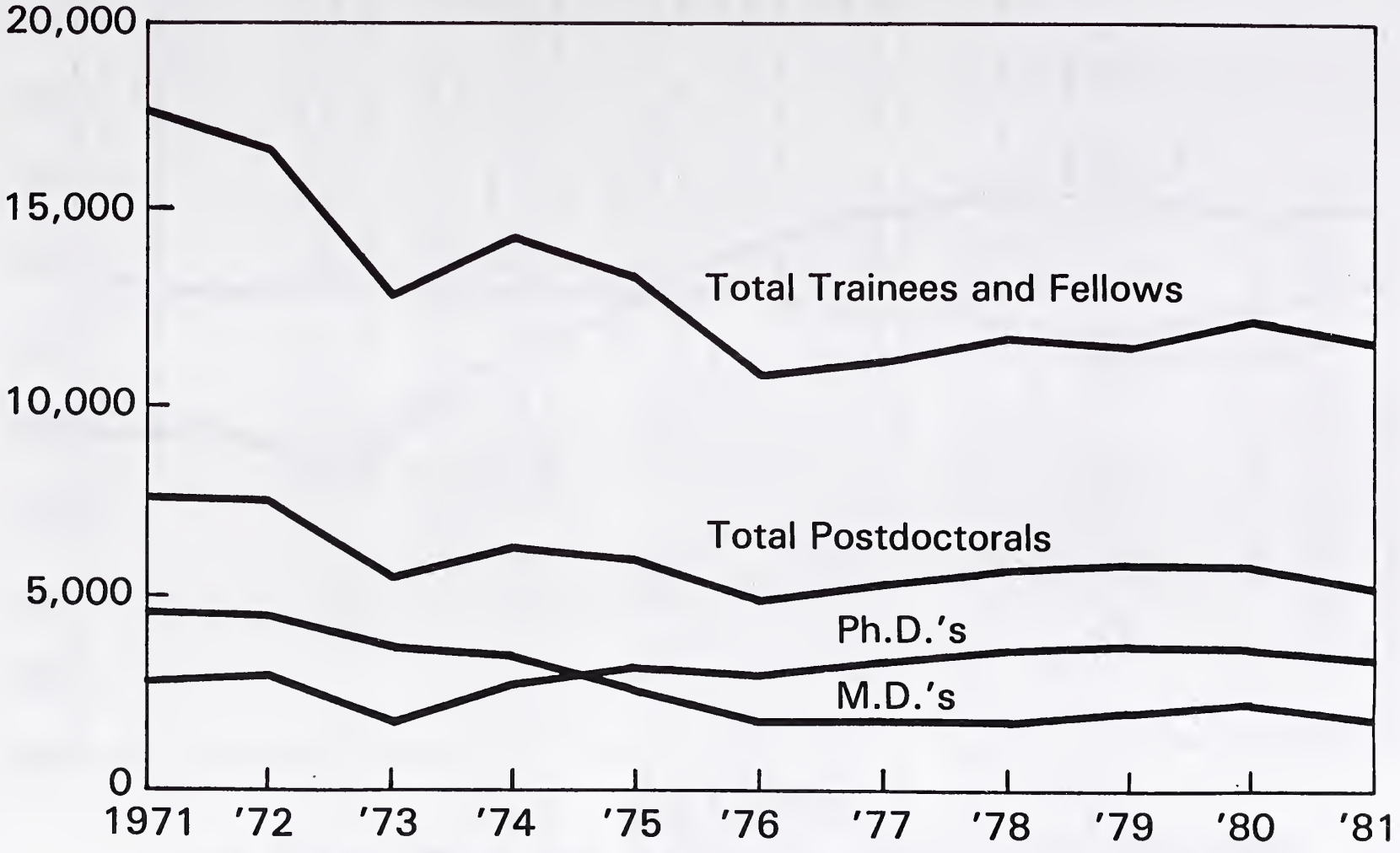
Total NIH Appropriations, 1972-83
In Current and Constant Dollars (Millions)




SUCCESS RATES OF NEW M.D., Ph.D., AND M.D./Ph.D.
APPLICANTS COMPARED WITH AVERAGE SUCCESS RATES O
ALL NEW R01 APPLICANTS IN THE SAME YEAR
PERCENT
160
150
140
130
120
110
100
90
80
70
M.D./Ph.D.
Ph.D.
M.D.
70
71
72
73
74
75
76
77
78
79
80
81
82
FISCAL YEAR

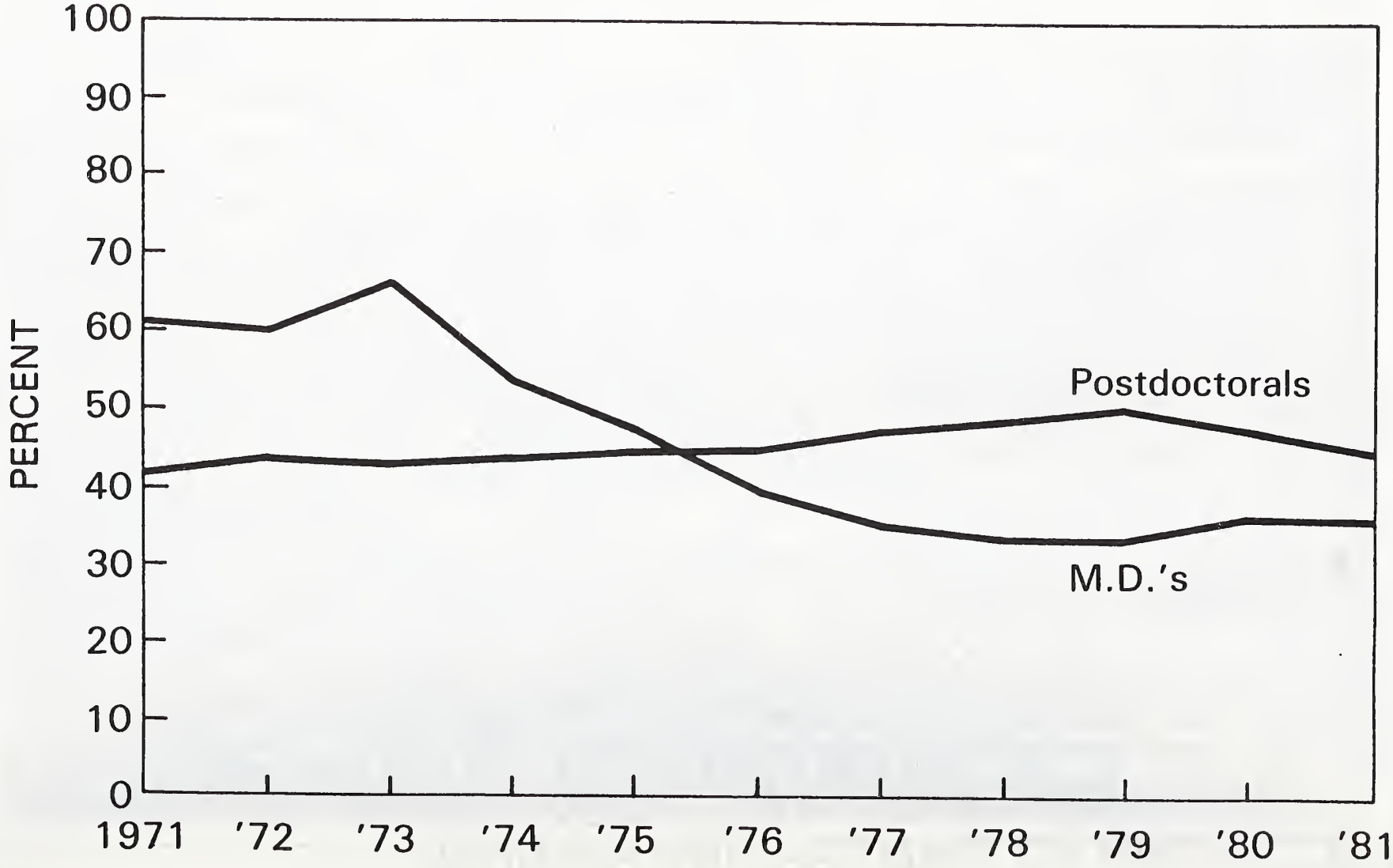
(5)

TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81



A-300

POSTDOCTORALS AS PERCENT OF TOTAL NIH TRAINEES AND FELLOWS, AND M.D.'S AS PERCENT OF TOTAL POSTDOCTORALS 1971-81



THE FUTURE OF CLINICAL INVESTIGATION*

by
James B. Wyngaarden, M.D.**

I CAN THINK OF NO MORE APPROPRIATE PLACE OR OCCASION TO DELIVER THIS LECTURE ON THE FUTURE OF CLINICAL INVESTIGATION THAN HERE AT THE CLEVELAND CLINIC IN HONOR OF DR. IRVINE PAGE. THE CLINIC IS AN EXCELLENT EXAMPLE OF AN ATMOSPHERE IN WHICH HIGH QUALITY RESEARCH, PATIENT CARE, AND TEACHING CAN FLOURISH. DR. PAGE--THROUGHOUT HIS ILLUSTRIOUS CAREER--HAS EPITOMIZED THE FINEST QUALITIES OF THE SCIENTIST, THE PHYSICIAN, THE EDUCATOR, AND THE WRITER.

I HAVE KNOWN IRV PAGE FOR MANY YEARS, THOUGH NOT AS WELL AS I WOULD HAVE LIKED TO KNOW HIM. WE SERVED TOGETHER FOR A TIME AS ADVISORS TO JACK WHITEHEAD WHEN JACK WAS FIRST TRYING TO PRECIPITATE HIS THOUGHTS ABOUT A WHITEHEAD INSTITUTE FOR MEDICAL RESEARCH, AND I ENJOYED THAT BRIEF ASSOCIATION. I KNEW, OF COURSE, OF DR. PAGE'S CONTRIBUTIONS TO HYPERTENSION, AND HIS DISCOVERY OF ANGIOTENSIN AND SEROTONIN, BUT I LEARNED MUCH MORE ABOUT IRV PAGE FROM A WONDERFUL ARTICLE IN THE JAMA IN 1980, ENTITLED "IRVINE H. PAGE, M.D.: NOT ONE MAN, BUT MANY."[1] IT IS AN UTTERLY IRREVERENT ARTICLE, ESPECIALLY WHERE THE AUTHOR QUOTES PAGE'S COMMENTS AND VIEWS ON HIMSELF. I PRESUME EVERYONE HERE HAS READ IT, BUT IF NOT, I COMMEND IT TO YOU.

THE RESEARCH COMMITMENT AND ACCOMPLISHMENTS HERE AT CLEVELAND CLINIC TO WHICH IRVINE PAGE MADE SUCH SEMINAL CONTRIBUTIONS ARE ILLUSTRATIVE OF THE FACT THAT A HEALTHY AND PRODUCTIVE CLINICAL RESEARCH EFFORT IS A MOSAIC OF ACHIEVEMENTS BY UNIVERSITIES, ACADEMIES, CLINICS, FOUNDATIONS, INDUSTRY, GOVERNMENT, AND THE SCIENTIFIC AND HEALTH PROFESSIONAL COMMUNITIES.

THERE IS PROBABLY LITTLE NEED TO CONVINCE AN AUDIENCE OF THIS NATURE OF THE IMPORTANCE OF CLINICAL RESEARCH, BUT SOMETIMES, ONE CANNOT HELP BUT BE STRUCK ANEW BY THE SIGNIFICANCE OF SPECIFIC CONTRIBUTIONS.

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*Irvine Page Lecture
Cleveland Clinic Foundation, June 24, 1983

**Director, National Institutes of Health, Bethesda, MD

I AM THINKING NOW OF THE TYPE OF RESEARCH DONE BY RECENT WINNERS OF THE HAZEN AWARD FOR CLINICAL RESEARCH: JESSE ROTH FOR EXPLAINING THE BASIC DEFECT IN CELL RECEPTORS IN DIABETES OF THE OBESE; HENRY KUNKLE FOR DEMONSTRATING THE ROLE OF CIRCULATING IMMUNE COMPLEXES IN DISEASE; AARON LERNER FOR EXPLAINING THE BIOLOGY OF BENIGN AND MALIGNANT PIGMENT CELLS; AND JOSEPH GOLDSTEIN AND MICHAEL BROWN FOR ELUCIDATING THE LDL RECEPTOR PATHWAY. OR ONE COULD CITE RECENT LASKER AWARD WINNERS IN CLINICAL RESEARCH, SUCH AS LAST YEAR'S RECIPIENTS--ELIZABETH NEUFELD FOR ELUCIDATING THE METABOLIC DEFECTS OF THE MUCOPOLYSACCHARIDOSES, AND ROSCOE BRADY FOR HIS CONTRIBUTIONS TO THE BIOCHEMISTRY AND EXPERIMENTAL THERAPY OF CERTAIN LIPID STORAGE DISEASES. AWARDS SUCH AS THESE RECOGNIZE OUTSTANDING EXAMPLES OF CLINICAL RESEARCH. IN THIS TYPE OF RESEARCH, THE CLINICAL QUESTION IS THE CENTRAL FORCE OF THE INVESTIGATION. THIS WORK IS A MOST EXCITING TYPE OF RESEARCH, REQUIRING SOMEONE WHO IS BOTH MEDICALLY KNOWLEDGEABLE AND SCIENTIFICALLY TRAINED. CLEARLY, THE CLINICAL INVESTIGATOR PROVIDES THE INDISPENSABLE LINK BETWEEN THE LABORATORY AND THE HUMAN BEING WHO IS THE ULTIMATE FOCUS OF ALL OF OUR ENDEAVORS.

IN THINKING ABOUT CLINICAL RESEARCH, WE OFTEN TEND TO FORGET A MAJOR BRANCH OF CLINICAL RESEARCH--CLINICAL TRIALS. BUT IT IS VERY CLEAR THAT OUR ABILITY TO MANAGE DISEASE WOULD STAGNATE IF SUCH WORK WERE NOT PURSUED. ILLUSTRATIVE IS THE WORK OF DRS. EMIL FREI III AND EMIL J FREIREICH, WHO RECENTLY RECEIVED THE 1983 CHARLES F. KETTERING PRIZE FOR CANCER RESEARCH FROM THE GENERAL MOTORS CANCER RESEARCH FOUNDATION. THESE SCIENTISTS, WHO BEGAN THEIR CAREERS TOGETHER AT THE NATIONAL CANCER INSTITUTE IN 1955, DEVELOPED OVER THE YEARS THE FIRST CURATIVE TREATMENT FOR CHILDHOOD LEUKEMIA AND, IN THE PROCESS, ESTABLISHED NEARLY ALL THE PRINCIPLES OF SCIENTIFIC CHEMOTHERAPY TRIALS FOR CANCERS OF ALL KINDS.

CLINICAL TRIALS, AS A TYPE OF CLINICAL RESEARCH, ARE EXPENSIVE AND TIME-CONSUMING. SOMETIMES THE GAINS SEEM SLOW IN COMING. WHEN FREI AND FREIREICH BEGAN THEIR CLINICAL STUDIES, LESS THAN ONE PERCENT OF PATIENTS LIVED LONG ENOUGH TO BE CONSIDERED CURED. TODAY, THE CURE RATE FOR CHILDHOOD LEUKEMIA IS ABOUT 56%. THESE STUDIES--GIVEN THEIR IMPACT ON THE TREATMENT OF LEUKEMIA AND THEIR IMPACT UPON CHEMOTHERAPY FOR OTHER TYPES OF CANCERS--WERE MAJOR CONTRIBUTIONS. WE NEED TO ENSURE THAT CLINICAL TRIALS CONTINUE TO MOVE BIOMEDICAL SCIENCE FROM THE BENCH TO THE BEDSIDE, BUT IN STRAINED ECONOMIC PERIODS, WE WILL HAVE TO SEEK COOPERATION WITH INDUSTRY, INCLUDING THE HEALTH INSURANCE INDUSTRY, AS WELL AS WITH OTHER AGENCIES OF GOVERNMENT THAT ARE CONCERNED WITH FINANCING OF HEALTH CARE, IN MEETING THE VERY LARGE COSTS OF CLINICAL TRIALS.

DR. DAVID A. HAMBURG, FORMER PRESIDENT OF THE INSTITUTE OF MEDICINE, PUT IT WELL WHEN HE SPOKE BEFORE A GROUP GATHERED IN 1980 TO DISCUSS NEEDS AND OPPORTUNITIES IN CLINICAL INVESTIGATION IN THE 1980'S: "WE MUST DO EVERYTHING IN OUR POWER TO SEE THAT THE GREAT FUNDAMENTAL ADVANCES--INDEED THE INSPIRING ADVANCES IN MOLECULAR AND CELLULAR BIOLOGY--WILL BE AVAILABLE AS SOON AS POSSIBLE FOR HEALTH INTERVENTIONS OF A DEMONSTRABLY USEFUL CHARACTER. BUT THE AUTHENTIC BIOLOGICAL REVOLUTION THAT HAS BEEN GENERATED BY SEVERAL DECADES OF INTENSIVE BASIC RESEARCH IS NOT EASILY TRANSLATED INTO CLINICALLY VALID APPLICATIONS. AN INTERPRETER IS NEEDED, AND IT IS THE CLINICAL INVESTIGATOR WHO SERVES THAT FUNCTION. THE FLOW OF INFORMATION IS BY NO MEANS UNIDIRECTIONAL; IF BASIC SCIENCE HAS SOMETHING TO SAY TO CLINICAL INVESTIGATION, SO TOO DOES CLINICAL INVESTIGATION OFFER MUCH TO BASIC SCIENCE. CLINICAL RESEARCH REMAINS THE VITAL BRIDGE BETWEEN ADVANCES IN BASIC SCIENCE ON THE ONE HAND AND IMPROVEMENTS IN HEALTH CARE--DIAGNOSTIC, THERAPEUTIC OR PREVENTIVE--ON THE OTHER."

DR. HAMBURG WENT ON TO SAY, "I WAS CONCERNED IN 1975, AND REMAIN CONCERNED TODAY, THAT THE INTERWOVEN FABRIC OF BASIC SCIENCE AND CLINICAL INVESTIGATION IS TO SOME EXTENT UNRAVELING."[2]

I WOULD LIKE TO EXAMINE HIS CONCERN, WHICH, TO SOME EXTENT, I SHARE. BUT I DO NOT BELIEVE THAT OUR CURRENT SITUATION REGARDING PHYSICIAN INVOLVEMENT IN RESEARCH CONSTITUTES A CRISIS. THAT WOULD BE AN EXAGGERATION. AVAILABLE DATA SHOW THAT THE SYSTEM IS IN A PERIOD OF ADJUSTMENT.

THE TWO-WAY FLOW I ALLUDED TO FROM BASIC SCIENCE TO CLINICAL APPLICATION AND FROM CLINICAL OBSERVATION TO BASIC SCIENCE DOES NOT SIMPLY OCCUR. IT REQUIRES INITIATION, PREPARATION, AND A CONDUCIVE INSTITUTIONAL ATMOSPHERE AND SUSTAINED SUPPORT. THE STAKES ARE SO HIGH AND THE SYSTEM SO DELICATE, THAT NURTURING OF THE ECOSYSTEM OF CLINICAL INVESTIGATION NEEDS THE ATTENTION OF THE GOVERNMENT AND THE PRIVATE SECTOR, INCLUDING INDUSTRY AND FOUNDATIONS.

WE--NIH AND THE SCIENTIFIC COMMUNITY-- NEED TO LOOK AT A NUMBER OF FACTORS THAT APPEAR TO BE CONTRIBUTING TO A DECLINING INTEREST IN CLINICAL INVESTIGATION ON THE PART OF YOUNG PHYSICIANS, INCLUDING: UNFAVORABLE SOCIAL CLIMATE (IN THE SOCIETY AT LARGE AND WITHIN MEDICAL SCHOOLS); LACK OF EARLY EXPOSURE TO RESEARCH; FUNDING CONSTRAINTS; TIME DEMANDS ON ACADEMIC PHYSICIANS; REGULATORY BURDENS; AND TENURE-ASSOCIATED PROBLEMS[3]. IN A COOPERATIVE EFFORT WE NEED TO EXAMINE WHAT MIGHT BE DONE TO ALLEVIATE SOME OF THESE STRAINS ON THE SYSTEM.

LET US LOOK AT SOME OF THE DATA SURROUNDING THIS ISSUE. (FIGURE 1)

THE ABSOLUTE NUMBER OF NIH RESEARCH GRANTS (RO1'S) AWARDED TO M.D.'S FELL FROM ABOUT 3,400 IN 1968 TO ABOUT 2,500 IN 1973. THERE HAS BEEN SOME RECOVERY SINCE, BUT THE NUMBER WAS STILL BELOW 3,000 IN 1982. THE NUMBER OF GRANTS TO MD/PH.D.'S (AND THESE ARE, OF COURSE, IN MUCH SMALLER NUMBERS) IS HOLDING RATHER STEADY. CONCURRENTLY, THERE HAS BEEN A STEADY RISE OF PH.D. PARTICIPATION WHICH COINCIDES WITH EXPANSION OF THE NATIONAL CANCER INSTITUTE AND THE LARGE THRUST INTO MANY AREAS OF BASIC SCIENCE GENERALLY.

(FIGURE 2) THE PERCENTAGE OF M.D.'S HOLDING NIH RESEARCH GRANTS HAS PROGRESSIVELY FALLEN OVER THE YEARS. M.D./PH.D.'S COMPRISE A RELATIVELY SMALL PROPORTION OF THE GRANT HOLDERS AND THIS GROUP HAS REMAINED RELATIVELY CONSTANT. CURRENTLY PH.D.'S HOLD APPROXIMATELY 68% OF THE NIH RESEARCH GRANT (RO1) PORTFOLIO WHILE M.D'S HOLD ONLY ABOUT 22 PERCENT. IF MD/PH.D.'S ARE ADDED, THE PERCENTAGE HELD BY THOSE WITH PROFESSIONAL DEGREES CLIMBS TO ABOUT 31%. ALTHOUGH THE PROPORTION OF RESEARCH GRANTS AWARDED TO M.D. INVESTIGATORS IS ABOUT ONE-HALF THAT OF A DECADE AGO, THE ABSOLUTE NUMBER OF AWARDS MADE TO PROFESSIONAL DEGREE HOLDERS HAS HELD FAIRLY STEADY. NIH CURRENTLY FUNDS MORE THAN 16,000 RO1 TYPE RESEARCH GRANTS, COMPARED WITH 9000 IN 1972. THE INCREMENT IN THE NUMBER OF SUCH GRANTS HAS GONE ALMOST ENTIRELY TO PH.D. APPLICANTS. MEANWHILE, MANY ADDITIONAL M.D.'S ARE PARTICIPATING IN OTHER RESEARCH MECHANISMS, SUCH AS SPECIALIZED RESEARCH CENTERS AND CLINICAL TRIALS.

IN A SIMPLE EXERCISE TO COMPARE THE NUMBERS OF M.D.'S ACTUALLY SUCCEEDING IN GETTING NIH GRANTS (RO1'S) AGAINST THE ENTIRE FIELD OF M.D.'S WHO COULD HAVE CHOSEN BIOMEDICAL RESEARCH FOR A CAREER, WE CONSTRUCTED THE NEXT SLIDE: (FIGURE 3).

THE NUMBER OF M.D.'S SERVING AS PRINCIPAL INVESTIGATORS ON NIH INVESTIGATOR-INITIATED GRANTS FROM 1968-1982 IS INDICATED BY THE SOLID LINE. AGAINST THAT IS PLOTTED THE NUMBER OF M.D. GRADUATES FOR EACH YEAR STARTING IN 1957. THE 11-YEAR OFFSET REFLECTS THE FACT THAT ON AVERAGE, THE M.D. IN RESEARCH DOES NOT RECEIVE HIS OR HER FIRST INDEPENDENT RESEARCH GRANT UNTIL 11 YEARS AFTER GRADUATION. AS THE SLIDE SHOWS, THE RATIO BETWEEN M.D. PRINCIPAL INVESTIGATORS AND THE NUMBER OF M.D. GRADUATES HAS NOT WIDENED VERY MUCH OVER THE YEARS SHOWN. THESE ROUGH DATA NEED TO BE VIEWED CAUTIOUSLY, HOWEVER. SINCE MEDICAL SCHOOL ENROLLMENT INCREASED DRAMATICALLY AFTER 1968, WE SUSPECT THAT THIS GAP MAY SOON WIDEN.

THE DECLINE IN THE PERCENTAGE OF M.D. INVESTIGATORS WORKING UNDER RO1 GRANTS REFLECTS THE SUBMISSION OF FEWER GRANT APPLICATIONS BY M.D. THAN PH.D. SCIENTISTS. IN 1970, M.D.'S COMPRISED ABOUT 30 PERCENT OF THE APPLICANTS; BY 1980, ONLY 24 PERCENT. ANOTHER IMPORTANT FACTOR IS THE INTENSE COMPETITION.

(TABLE I) FOR ALL COMPETING RESEARCH GRANT APPLICATIONS, APPROVAL AND AWARD RATES DID NOT DIFFER GREATLY FOR M.D. AND PH.D. APPLICANTS BETWEEN 1974 AND 1982. THE APPROVAL RATE FOR APPLICATIONS SUBMITTED BY PH.D. INVESTIGATORS HAS RUN ONLY THREE OR FOUR PERCENTAGE POINTS AHEAD OF RATES FOR M.D. INVESTIGATORS. OF THE GRANTS APPROVED BY STUDY SECTIONS, THE AWARD RATES (THAT IS, THE CHANCE OF GETTING FUNDED ONCE APPROVED) FOR M.D. AND PH.D. PRINCIPAL INVESTIGATORS IS VIRTUALLY THE SAME.

(FIGURE 4) HOWEVER, WHEN ONE LOOKS AT THE SUCCESS RATE OF NEW APPLICANTS ALONE, ONE FINDS THAT THERE HAS BEEN A DIVERGENCE SINCE ABOUT 1974, WITH NEW M.D. APPLICANTS COMPETING LESS WELL THAN NEW PH.D. APPLICANTS, WITH BOTH GROUPS COMPETING LESS SUCCESSFULLY THAN THE MD/PH.D. APPLICANT.

(FIGURE 5) THIS TREND IS EVEN MORE DRAMATIC WHEN EXPRESSED IN COMPARISON WITH THE AVERAGE SUCCESS RATE OF ALL RESEARCH GRANT APPLICATIONS OF THAT YEAR, WHICH HAS BEEN GIVEN A SCORE OF 0. NOTE THAT INCREASINGLY, THE GREATEST SUCCESS IS OBTAINED BY THE MD/PH.D. APPLICANT, FOLLOWED BY THE PH.D. APPLICANT AT SOMEWHAT ABOVE THE AVERAGE RATE, AND BY THE M.D. APPLICANT WHO IS INCREASINGLY BELOW THE AVERAGE RATE.

ONE FACTOR THAT MAY BE PLAYING A ROLE IN THE RECORD FOR M.D. APPLICANTS IS THE FACT THAT APPLICATIONS FOR CLINICAL RESEARCH TEND TO FARE LESS WELL THAN BASIC SCIENCE APPLICATIONS IN THE NIH GRANT REVIEW SYSTEM.

CLINICAL RESEARCH APPLICATIONS--THOSE INVOLVING HUMAN SUBJECTS OR HUMAN TISSUES--ARE MORE OFTEN DISAPPROVED AND MORE OFTEN ASSIGNED POORER PRIORITY SCORES THAN ARE APPLICATIONS IN WHICH NO HUMAN SUBJECTS ARE INVOLVED.

AS THE NEXT TABLE INDICATES, (TABLE II), APPROVAL RATES FOR STUDIES WHICH DON'T INVOLVE HUMAN SUBJECTS ARE SUBSTANTIALLY HIGHER THAN THOSE FOR STUDIES WITH HUMAN SUBJECTS, REGARDLESS OF WHETHER THE PRINCIPAL INVESTIGATOR IS AN M.D. OR A PH.D.

IN ORDER TO DISCOVER WHY APPLICATIONS TO NIH FOR GRANTS TO CONDUCT CLINICAL RESEARCH MAY EITHER BE DISAPPROVED OR RECEIVE POOR PRIORITY IN THE REVIEW PROCESS, THE DIVISION OF RESEARCH GRANTS EXAMINED 256 APPLICATIONS RATED BY 13 DIFFERENT STUDY SECTIONS.[4] (TABLE III) FOR THIS STUDY, CLINICAL RESEARCH WAS NARROWLY DEFINED AS RESEARCH INVOLVING HUMAN SUBJECTS THAT INCLUDED A DOCTOR-PATIENT RELATIONSHIP. IT IS INTERESTING AND IMPORTANT TO NOTE THAT INVESTIGATOR QUALIFICATIONS AND RESOURCES AT THEIR INSTITUTIONS PLAYED A VERY MINOR ROLE IN POOR RATING. FLAWS IN RESEARCH DESIGN AND CONCEPTION OF THE HYPOTHESIS LED TO POOR SCORES FROM REVIEWERS. THE MOST FREQUENT DEFICIENCIES--FAULTY HYPOTHESES AND INAPPROPRIATE EXPERIMENTAL DESIGN--WERE THE SAME FLAWS THAT WERE CITED IN THE BASIC RESEARCH PROPOSALS THAT ARE DISAPPROVED.

THE FACILE EXPLANATION OF THE GREATER DIFFICULTY INHERENT IN WORKING WITH HUMAN SUBJECTS MAY NOT BE THE ENTIRE ANSWER TO THE LOWER APPROVAL RATES FOR PHYSICIAN-INVESTIGATORS. SCIENCE HAS BECOME COMPLEX, THE METHODS INTRICATE AND THE TRAINING PERIOD SO LONG THAT THE PHYSICIAN, EVEN AFTER TWO OR THREE YEARS OF FELLOWSHIP TRAINING, REMAINS LESS WELL-TRAINED THAN THE PH.D. SCIENTIST WHO HAS BEEN TRAINING FOR A RESEARCH CAREER SINCE THE BACCALAUREATE. IN MY VIEW, THE TRENDS OF THE PAST DECADE REFLECT THE PROGRESSIVE PROFESSIONALIZATION OF BIOMEDICAL RESEARCH, IN PARTICULAR OF CLINICAL RESEARCH. I HOPE THERE WILL ALWAYS BE ROOM FOR THE CREATIVE AMATEUR IN CLINICAL INVESTIGATION, BUT RECENT HISTORY INDICATES THAT SUCH A PERSON IS LESS AND LESS LIKELY TO SECURE EXTERNAL SUPPORT FOR HIS OR HER WORK. SUCCESS FOR AN M.D. INVESTIGATOR IS INCREASINGLY DEPENDENT UPON SUBSTANTIAL TRAINING IN THE INFORMATION, CONCEPTS, AND METHODOLOGIES OF COMPLEX MODERN SCIENCE. TO BE A FIRST-RATE SCIENTIST AND A WELL-QUALIFIED PHYSICIAN IS A DEMANDING CALLING.

MOREOVER, CLINICAL RESEARCH REQUIRES EXPERIENCES NOT REPRESENTED IN MOST MEDICAL SCHOOL AND HOUSE STAFF EXPERIENCES. THE QUALITY OF A RESEARCH GRANT IS A REFLECTION OF THE COMPETENCE AND SOPHISTICATION OF THE INVESTIGATOR APPLICANT. AS DAMON RUNYON SAID, "THE RACE IS NOT ALWAYS TO THE SWIFT OR THE BATTLE TO THE STRONG, BUT THAT'S THE WAY TO BET."

THE INTEGRAL RELATIONSHIP BETWEEN TRAINING AND LATER CONDUCT OF RESEARCH SEEMS ALMOST SELF-EVIDENT, BUT I WOULD LIKE TO CITE SEVERAL PIECES OF DATA THAT SUPPORT THIS CONTENTION. ONE STUDY BY THE AAMC[5] HAS SHOWN THAT FOR BOTH M.D.'S AND PH.D.'S, POSTDOCTORAL TRAINING HAS THE GREATEST INFLUENCE ON APPROVAL RATE ON FIRST RESEARCH GRANT APPLICATIONS, WITH OTHER SIGNIFICANT FACTORS BEING THE INSTITUTION CONFERRING THE DEGREE AND THE PLACE OF EMPLOYMENT.

(TABLE IV) A RECENT REVIEW OF NIH GRANT FILES[6] INDICATES THE WORTH OF NRSA TRAINING FOR BOTH POST-M.D. AND POST-PH.D. APPLICANTS. THIS ANALYSIS FOUND THAT M.D.'S WITH NIH-SUPPORTED TRAINING HAD AN AVERAGE SUCCESS RATE OF 36.5 PERCENT VERSUS 25 PERCENT FOR M.D.'S WITHOUT SUCH TRAINING. A SIMILARLY LARGE DIFFERENCE BASED ON TRAINING WAS FOUND IN THE AVERAGE SUCCESS RATES FOR PH.D.'S.

BECAUSE OF THE ESTABLISHED PRIMACY OF POSTDOCTORAL TRAINING IN ENHANCING THE PARTICIPATION OF PHYSICIAN INVESTIGATORS IN INDEPENDENT RESEARCH, IT IS IMPORTANT TO LOOK AT THE STATUS OF NIH TRAINING LEVELS IN ORDER TO ASSESS ACCURATELY THE FUTURE PICTURE FOR CLINICAL RESEARCH.

THE NUMBERS OF M.D. TRAINEES AND FELLOWS FELL FROM ABOUT 4,600 TO ABOUT 1,900 BETWEEN FY 1971 AND 1981. THIS SEEMINGLY DRASTIC DECLINE IS SOMEWHAT ARTIFICIAL BECAUSE CESSATION OF FEDERAL SUPPORT FOR CLINICAL TRAINING IN THE EARLY 1970'S CERTAINLY CONTRIBUTED TO THE DROP-OFF.

(FIGURE 6) DATA FROM 1975 TO THE PRESENT CORRESPOND TO THE INCEPTION AND DEVELOPMENT OF THE NATIONAL RESEARCH SERVICE AWARD (NRSA) PROGRAM. WE SEE THE DECLINE IN M.D. PARTICIPATION CONTINUING TO FY 1976 AND THEN APPARENTLY LEVELING OFF. AT THE SAME TIME, PH.D. PARTICIPATION HAS GREATLY INCREASED.

THE MODIFICATION IN AUTHORITY IN 1974, UNDER THE NATIONAL RESEARCH SERVICE AWARDS ACT, LIMITS TRAINING EXCLUSIVELY TO RESEARCH OR ACADEMIC DEVELOPMENT. UNDER THE SAME ACT, A COMMITTEE OF THE NATIONAL ACADEMY OF SCIENCES HAS RECOMMENDED THAT 2,800 CLINICAL RESEARCH TRAINING SLOTS BE OFFERED BY NIH ANNUALLY--2,400 AS TRAINEESHIPS, AND 400 AS DIRECT FELLOWSHIPS. THIS FIGURE OF 2,800 CLINICAL TRAINING POSITIONS WAS NOT REACHED UNTIL 1980, BUT AT THAT TIME 900 OF THESE CLINICAL TRAINEESHIPS WERE HELD BY PH.D. TRAINEES, (TWICE THE NUMBER ONLY THREE YEARS AGO) AND ONLY 1,900 BY M.D. TRAINEES. THE ACADEMY COMMITTEE HAS RECOMMENDED THAT AT LEAST 85 PERCENT OF THE TRAINEESHIPS IN THIS CATEGORY OR ABOUT 2,400 BE FILLED BY M.D.'S. SO, BY EVERY YARDSTICK, WE ARE FAILING TO ATTRACT THE NUMBER OF QUALIFIED PHYSICIANS INTO RESEARCH TRAINING PERCEIVED TO BE DESIRABLE BY THE ACADEMY COMMITTEE. FORTUNATELY, SOME OF THIS GAP IS BEING FILLED BY PH.D. SCIENTISTS INTERESTED IN CLINICAL RESEARCH. BUT THIS SHORTFALL OF PHYSICIAN INVESTIGATORS ALTERS THE BALANCE BETWEEN M.D. AND PH.D. INVESTIGATORS DEEMED ESSENTIAL FOR COORDINATED PROGRESS IN BASIC SCIENCE AND CLINICAL RESEARCH.

MANY REASONS HAVE BEEN CITED FOR THE DECLINING INTEREST OF PHYSICIANS IN CLINICAL RESEARCH. MOST MEDICAL SCHOOL CURRICULA PROVIDE LITTLE OR NO LABORATORY EXPERIENCE THAT IS REPRESENTATIVE OF MODERN DAY MEDICAL SCIENCE. THE RISE OF SPECIALTY FIELDS AND THE LENGTHENING OF POSTDOCTORAL TRAINING PROGRAMS HAVE EXTENDED THE CLINICAL TRAINING NECESSARY FOR BOARD CERTIFICATION. THE REQUIREMENTS OF MANY CERTIFICATION BOARDS ARE RATHER INFLEXIBLE AND CERTAINLY DO NOT ENCOURAGE THE POTENTIALLY CREATIVE PHYSICIAN TO ENTER RESEARCH TRAINING.

OTHER CONSIDERATIONS MAY ACT AS DETERRENTS FOR SOME POTENTIAL TRAINEESHIP APPLICANTS. PERHAPS DOMINATING THE ISSUES IS THAT OF THE FINANCIAL DISINCENTIVES, BOTH BETWEEN THE THIRD-YEAR RESIDENCY SALARY AND THE FIRST-YEAR TRAINEESHIP, WHICH NOW EXHIBITS AN AVERAGE GAP OF $6,000, AND THE SUBSTANTIALLY LARGER DIFFERENCES BETWEEN THE INCOME POSSIBILITIES IN RESEARCH AND IN PROCEDURE-ORIENTED PRACTICES OF MEDICINE. AND ESPECIALLY WHEN THE DEBT LOAD INCURRED BY THE GRADUATING STUDENT IS $20,000 OR MORE, THE CUMULATIVE FINANCIAL DISINCENTIVES ARE A MAJOR FACTOR IN DISSUADING POTENTIAL INVESTIGATORS FROM ENTERING THE FIELD.

FORTUNATELY, THIS GROWING PROBLEM HAS RECEIVED CONSIDERABLE ATTENTION IN THE CONGRESS. EARLIER THIS YEAR WE RECEIVED THE REPORT OF THE HOUSE COMMITTEE ON APPROPRIATIONS REGARDING THE PROPOSED 1983 BUDGET FOR THE NIH[7]. PERMIT ME TO READ A PARAGRAPH:

> "THE COMMITTEE SHARES THE CONCERNS THAT HAVE BEEN EXPRESSED BY OFFICIAL AND PUBLIC WITNESSES ABOUT THE DIFFICULTY OF RECRUITING AND RETAINING PHYSICIANS FOR RESEARCH CAREERS, ESPECIALLY AS ALL CLINICAL RESEARCH, INVOLVING HUMAN PATIENTS, MUST BE DONE BY--OR AT LEAST UNDER THE GUIDANCE AND SUPERVISION OF--A QUALIFIED PHYSICIAN. IT IS APPARENT AND UNDERSTANDABLE, THAT YOUNG PHYSICIANS CONSIDERING CAREERS IN HEALTH RESEARCH ARE OFTEN DISSUADED FROM APPLYING FOR RESEARCH TRAINING OR RESEARCH FELLOWSHIPS BY THEIR PERCEPTION OF THE INSTABILITY OF THE FEDERAL COMMITMENT TO RESEARCH AND BY THEIR AWARENESS THAT A RESEARCH CAREER REPRESENTS A SUBSTANTIAL FINANCIAL SACRIFICE WHEN COMPARED WITH ALMOST ANY FORM OF MEDICAL PRACTICE."

THE COMMITTEE WENT ON TO REQUEST A REPORT ON OUR PLANS FOR DEALING WITH THIS SHORTAGE OF PHYSICIANS IN RESEARCH.

EVEN WITHOUT CONGRESSIONAL PRODDING, NIH HAS DEVOTED CONSIDERABLE ATTENTION TO THIS PROBLEM AND HAS UNDER CONSIDERATION SOME MAJOR STEPS TOWARD ITS SOLUTION.

AT THE UNDERGRADUATE MEDICAL STUDENT LEVEL, WE HAVE CONTINUED TO GIVE THE MEDICAL SCIENTIST TRAINING PROGRAM (MSTP) TOP PRIORITY IN OUR TRAINING PORTFOLIO.

IN THE MSTP THIS YEAR, WE WILL SUPPORT ABOUT 650 STUDENTS MOVING TOWARD A COMBINED M.D./PH.D. DEGREE. WE REGARD THIS PROGRAM AS ONE OF OUR MOST SUCCESSFUL IN TERMS OF BUILDING UP CLINICAL RESEARCH. THIS SIX-YEAR PROGRAM, SPONSORED BY THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES, MAKES AWARDS TO 24 SCHOOLS FOR STUDENTS WHO SIMULTANEOUSLY EARN THE M.D. AND PH.D. DEGREES. FOLLOW UP EVALUATION OF THE PROGRAM HAS SHOWN THAT 70 PERCENT OF THE GRADUATES HOLD POSITIONS IN ACADEMIC MEDICINE DOING RESEARCH AND ENGAGING IN THE TRAINING OF OTHER PHYSICIANS. THE PROGRAM WILL BE STRENGTHENED TO SUPPORT APPROXIMATELY 700 STUDENTS PER YEAR, RESULTING IN PRODUCTION OF MORE THAN 100 GRADUATES PER YEAR OF THE TYPE OF SCIENTIST CURRENTLY COMPETING MOST SUCCESSFULLY FOR R01 RESEARCH SUPPORT.

THE NIH HAS A NUMBER OF PROGRAMS THAT PROVIDE EARLY EXPOSURE TO RESEARCH CAREERS. THIS PAST YEAR MORE THAN 1,100 MEDICAL STUDENTS AVAILED THEMSELVES OF OFF-QUARTER TRAINING OPPORTUNITIES SUPPORTED BY NIH. WITH THE NEW EXEMPTION OF

THE FIRST YEAR OF NRSA SUPPORT FROM PAYBACK OBLIGATION, THE NIH LAST YEAR REINSTITUTED THE POST-SOPHOMORE FELLOWSHIP OR ITS EQUIVALENT, TO PROVIDE A FULL YEAR OF RESEARCH TRAINING WITHIN THE MEDICAL SCHOOL EXPERIENCE UNDER AN NIH FELLOWSHIP OR TRAINEESHIP. THE NIH ALSO OFFERS SUMMER RESEARCH FELLOWSHIPS AT BETHESDA, AND DURING THIS PAST YEAR 52 MEDICAL STUDENTS PARTICIPATED IN THAT PROGRAM.

THE PHYSICIAN WHO HAS COMPLETED FOUR YEARS OF MEDICAL SCHOOL AND ONE-TO-THREE YEARS OF CLINICAL TRAINING IS, BY AND LARGE, ONLY MODESTLY PREPARED WITH RESEARCH SKILLS. EVEN WHERE SUCCESSFUL PARTICIPATION IN ONE OR MORE RESEARCH PROJECTS HAS TAKEN PLACE, THE EXPERIENCE DOES NOT SUBSTITUTE FOR A PLANNED PROGRAM TO DEVELOP RESEARCH EXPERTISE. A SERIES OF NIH AWARDS, CALLED CAREER DEVELOPMENT AWARDS, PROVIDE RESEARCH DEVELOPMENT OPPORTUNITIES TO QUALIFIED INDIVIDUALS WITH DEMONSTRATED RESEARCH POTENTIAL. TWO MECHANISMS HAVE BEEN PARTICULARLY SUCCESSFUL IN THE ATTRACTION OF PHYSICIANS--THE CLINICAL INVESTIGATOR AWARD AND THE SPECIAL EMPHASIS RESEARCH CAREER AWARD. BOTH PROVIDE FOR 3-5 YEARS OF SUPERVISED RESEARCH DEVELOPMENT IN AREAS OF IMMEDIATE INTEREST TO THE FUNDING INSTITUTE. THEY PROVIDE UP TO $30,000 PER YEAR IN SALARY PLUS COMMENSURATE FRINGE BENEFITS AND SOME MODEST AMOUNT OF RESEARCH SUPPORT. THESE PROGRAMS HAVE BEEN SUCCESSFUL AND THUS HAVE DEMONSTRATED A POTENTIAL FOR EXPANSION.

THE NEWEST ADDITION TO THE CAREER DEVELOPMENT AWARD SERIES WILL BE ANNOUNCED IN JULY. THIS "PHYSICIAN- SCIENTIST" AWARD IS DESIGNED TO PROVIDE FIVE YEARS OF PHASED SUPERVISED RESEARCH TRAINING. THE FIRST 2-3 YEARS WILL BE UNDER THE GUIDANCE OF A SPONSOR WHO IS A BASIC SCIENTIST. THE AWARD WILL CARRY A SALARY COMPARABLE TO THAT EARNED BY A MEMBER OF THE INSTITUTION'S HOUSE STAFF WITH EQUIVALENT EXPERIENCE, UP TO TEN PERCENT OF THE BASIC SCIENCE SPONSOR'S SALARY AND $10,000 FOR RESEARCH COSTS. THE SECOND PHASE, UNDERTAKEN AT A MORE INDEPENDENT LEVEL, WILL PROVIDE UP TO $20,000 TO COVER RESEARCH COSTS. THE PROGRAM WILL BE SPONSORED BY SEVEN NIH INSTITUTES. IT COMPLEMENTS THE MSTP PROGRAM IN PROVIDING GRADUATE SCHOOL LEVEL EXPERIENCE FOR THE PROFESSIONAL DEGREE HOLDER WHO BEGINS AT A POST-MEDICAL SCHOOL STAGE.

BUT THE WISDOM OF UNDERTAKING RESEARCH TRAINING COULD EASILY BE QUESTIONED BY A YOUNG PHYSICIAN IF THE OPPORTUNITY TO ENGAGE IN SUPPORTED RESEARCH IN THE FUTURE IS HIGHLY UNCERTAIN. ONE MAJOR FACTOR IMPACTING UPON A YOUNG PHYSICIAN'S DECISION IS HIS OR HER PERCEPTION OF THE LONG-TERM STABILITY OF FEDERAL SUPPORT OF RESEARCH. THIS IS ONE REASON FOR NIH'S CONTINUED EMPHASIS ON THE NEED TO "STABILIZE" OUR OFFERING OF GRANTS FOR INVESTIGATOR-INITIATED PROJECT RESEARCH--TO PROVIDE A REASONABLE DEGREE OF ASSURANCE ABOUT FUTURE OPPORTUNITIES. THE POLICY OF FUNDING A MINIMUM OF 5,000 NEW AND COMPETING AWARDS HAS HELPED, WE

BELIEVE, TO STABILIZE EMERGING RESEARCH CAREERS. CURRENTLY 50 PERCENT OF NEW AWARDS AND 10 PERCENT OF ALL AWARDS ARE MADE TO FIRST-TIME APPLICANTS, NOT BY ALLOCATION BUT ON THE BASIS OF OPEN COMPETITION.

ANOTHER NIH PROGRAM--SO WELL-ESTABLISHED THAT IT OFTEN IS OVERLOOKED--IS A MAJOR CONTRIBUTOR TO THE STRENGTH OF CLINICAL RESEARCH IN THIS COUNTRY. THIS IS THE GENERAL CLINICAL RESEARCH CENTERS PROGRAM OF THE DIVISION OF RESEARCH RESOURCES, ESTABLISHED IN 1959 THROUGH ACTION OF THE SENATE APPROPRIATIONS COMMITTEE, WHICH EXPRESSED THE BELIEF THAT NATIONAL CLINICAL RESEARCH RESOURCES WERE INADEQUATE. TODAY, MORE THAN 3,000 PROJECTS ARE CONDUCTED IN THE CENTERS EACH YEAR BY AN EVEN GREATER NUMBER OF INVESTIGATORS, MOST OF WHOM ARE SUPPORTED THROUGH VARIOUS TYPES OF NIH AWARDS. IN 1982, THERE WERE 74 CENTERS WITH 595 RESEARCH BEDS AND 119,361 OUTPATIENT VISITS.

IN THE BEGINNING OF MY TALK I MENTIONED THE IMPORTANCE OF MAINTAINING A LEVEL OF CLINICAL TRIALS IN THIS COUNTRY IN THE FACE OF RISING COSTS OF SUCH UNDERTAKINGS. THIS IS AN AREA OF CLINICAL INVESTIGATION WHICH MUST BE MET WITH NEW AND CREATIVE MANAGEMENT. A PROGRAM RECENTLY INAUGURATED BY THE NCI--THE COMMUNITY CLINICAL ONCOLOGY PROGRAM--IS AN EXAMPLE OF INNOVATION ACCOMPLISHED THROUGH THE COOPERATIVE EFFORT OF THE NIH AND THE SCIENTIFIC AND MEDICAL COMMUNITY. THE PROGRAM IN 59 LOCATIONS AROUND THE COUNTRY--INCLUDING FOUR OHIO CITIES--INVOLVES COMMUNITY PHYSICIANS AFFILIATING WITH MAJOR MEDICAL CENTERS TO PARTICIPATE IN CANCER CLINICAL TRIALS. BY INCREASING SUBSTANTIALLY THE NUMBER OF PATIENTS IN TREATMENT STUDIES, THE PROGRAM WILL REDUCE THE TIME NEEDED TO COMPLETE CLINICAL TRIALS AND HASTEN TRANSFER OF NEW TECHNOLOGIES TO THE LOCAL LEVEL. THE PROGRAM IS POSSIBLE ONLY BECAUSE OF THE GROWTH OF THE FIELD OF MEDICAL ONCOLOGY IN THIS COUNTRY--A FIELD WHICH INCREASED DUE TO THE NATIONAL CANCER ACT FROM ABOUT 100 INDIVIDUALS IN 1970 TO ABOUT 3,000 BOARD CERTIFIED SPECIALISTS TODAY--AND BECAUSE THESE SPECIALISTS ENCOURAGED THEIR OWN CONTINUED INVOLVEMENT IN CLINICAL INVESTIGATION.

WHILE NIH PROGRAMS AND POLICIES WILL UNDOUBTEDLY HAVE A MAJOR IMPACT UPON THE FUTURE OF CLINICAL INVESTIGATION IN THIS COUNTRY, MAINTENANCE AND GROWTH OF THIS FIELD <u>IS</u> THE OBLIGATION OF ACADEMIC MEDICINE, THE MEDICAL PROFESSION AS A WHOLE, INDUSTRY, AND OTHER PARTS OF THE PRIVATE SECTOR, AS WELL AS GOVERNMENT. SOME MEDICAL SCHOOLS--FOR EXAMPLE, CASE WESTERN RESERVE, DUKE UNIVERSITY, UNIVERSITY OF PENNSYLVANIA, AND OTHERS--HAVE DEVELOPED CURRICULA WITH THE ASPIRING CLINICAL INVESTIGATOR IN MIND. PRIVATE SECTOR ENTITIES SUCH AS THE AMERICAN CANCER SOCIETY AND THE AMERICAN HEART ASSOCIATION HAVE ESTABLISHED SPECIAL AWARDS FOR PHYSICIAN SCIENTISTS. ALL OF THESE EFFORTS CONTINUE TO MITIGATE THE CIRCUMSTANCES WHICH SEEM TO BE HINDERING THE GROWTH OF CLINICAL INVESTIGATION.

IN ADDITION, THE CURRENT GENERATION OF CLINICAL INVESTIGATORS HAS A SPECIAL RESPONSIBILITY TO PORTRAY THE SATISFACTIONS THAT CAN COME FROM CLINICAL RESEARCH AS A CAREER. WE NEED TO LET STUDENTS KNOW THAT IN CLINICAL RESEARCH THERE IS OPPORTUNITY TO BE A CAPABLE AND CARING CLINICIAN, AND ALSO TO SHARE IN THE EXCITEMENT THAT COMES FROM DISCOVERY.

BEYOND THE PERSONAL GRATIFICATION THAT COMES FROM CREATIVE WORK, CLINICAL RESEARCH OFFERS THE CHANCE TO CONTRIBUTE BOTH TO THE HEALTH OF INDIVIDUAL PATIENTS, AND OF GROUPS OF PEOPLE. WE MUST KEEP STRESSING THAT FOR THOSE EXCEPTIONAL STUDENTS WHO WILL TAKE ON THE CHALLENGE OF RESEARCH, THE REWARDS ARE GREAT.

I BELIEVE THAT OUR OWN WORDS AND ACTIONS AS CLINICAL INVESTIGATORS ARE CRITICAL TO THE FUTURE OF OUR PROFESSION. IN HIS BOOK, "EXCELLENCE: CAN WE BE EQUAL AND EXCELLENT TOO?", JOHN GARDNER REMARKED THAT THE INFLUX OF EXCELLENT NEW PEOPLE INTO A GIVEN FIELD IN LARGE PART DEPENDS UPON THE MORALE OF THAT FIELD.[8] AND A MAJOR COMPONENT OF OUR COLLECTIVE MORALE IS THE OPTIMISM AND ENCOURAGEMENT WE PORTRAY TO NEWCOMERS AND THOSE ON THE BRINK OF DECISION.

I HOPE I HAVE MADE A CONTRIBUTION TO OPTIMISM THIS AFTERNOON IN CITING THE CONTINUING COMMITMENT OF NIH TO THE TRAINING, DEVELOPMENT AND RESEARCH SUPPORT OF THE CLINICAL INVESTIGATOR.

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[1]"Irvine H. Page, M.D.: Not One Man, But Many," Journal of the American Medical Association, Oct. 17, 1980, Vol. 244, No. 16, pp. 1765-1766, 1771-1772.

[2]Conference Summary, "Clinical Investigations in the 1980s; Needs and Opportunities," June, 1981, National Institute of Medicine, National Academy Press, p. 2.

[3]As above, pp. 8-13.

[4]Janet Cuca, "NIH Grant Applications for Clinical Research: Reasons for Poor Ratings or Disapprobal," Division of Research Grants, NIH, September 1982.

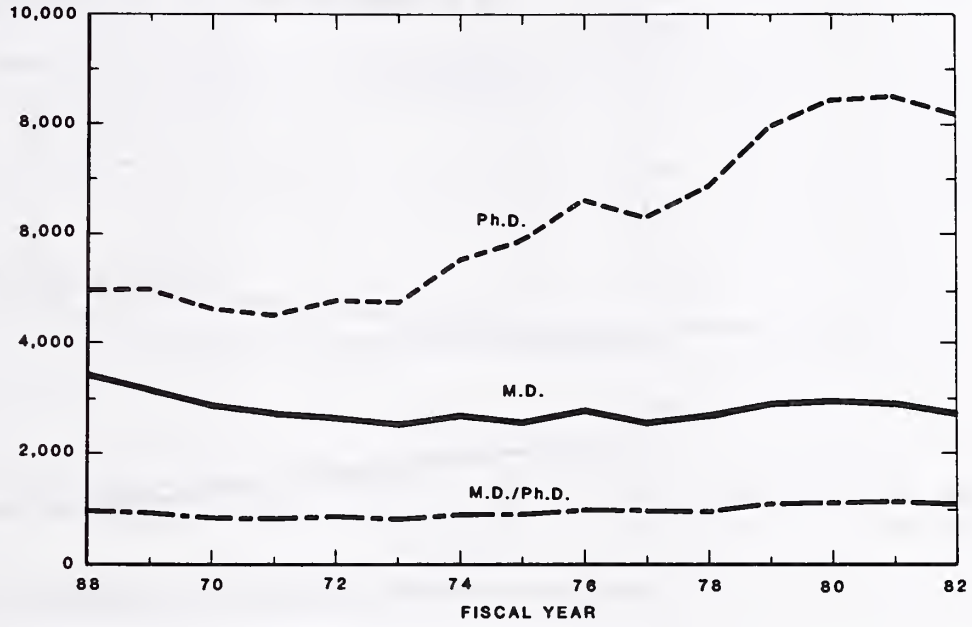
[5]Charles R. Sherman, Ph.D., and Thomas E. Morgan, M.D. "Education Patterns and Research Grants Success of Medical School Faculty." An evaluation study prepared for the NIH by the Association of American Medical Colleges, January 1979.

[6]Office of Program Analysis Note No. 6, "Competing Grant Applications from NRSA Trainees," Office of Program Planning and Evaluation, Office of the Director, NIH, October, 1982.

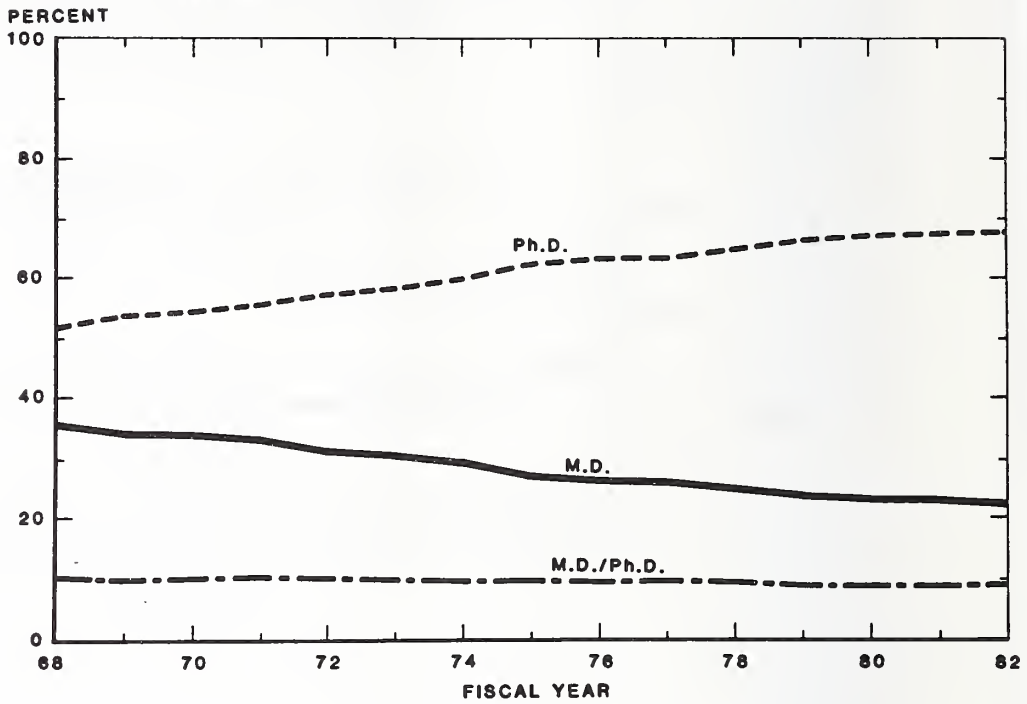
[7]Report No. 97-894, 97th Congress, 2nd Session, House of Representatives, "Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 1983," September 29, 1982.

[8]John W. Gardner, "Excellence: Can We Be Equal and Excellent Too?" Harper & Row, Publishers, New York and Evanston, 1961.

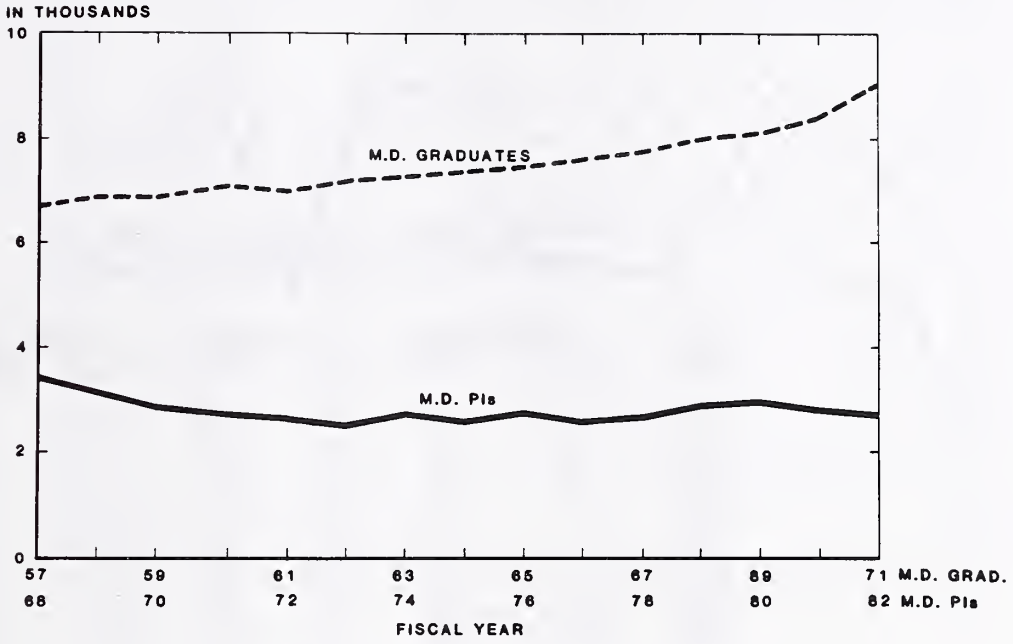
NUMBER OF PIs WITH M.D., Ph.D., OR M.D./Ph.D. DEGREES ON ALL R01 GRANTS



PIs WITH M.D., Ph.D., OR M.D./Ph.D. DEGREES
AS A PERCENT OF ALL PIs ON R01 GRANTS



NUMBER OF M.D. PIs ON ALL R01 GRANTS COMPARED WITH NUMBER OF M.D.'s WHO GRADUATED 11 YEARS BEFORE *

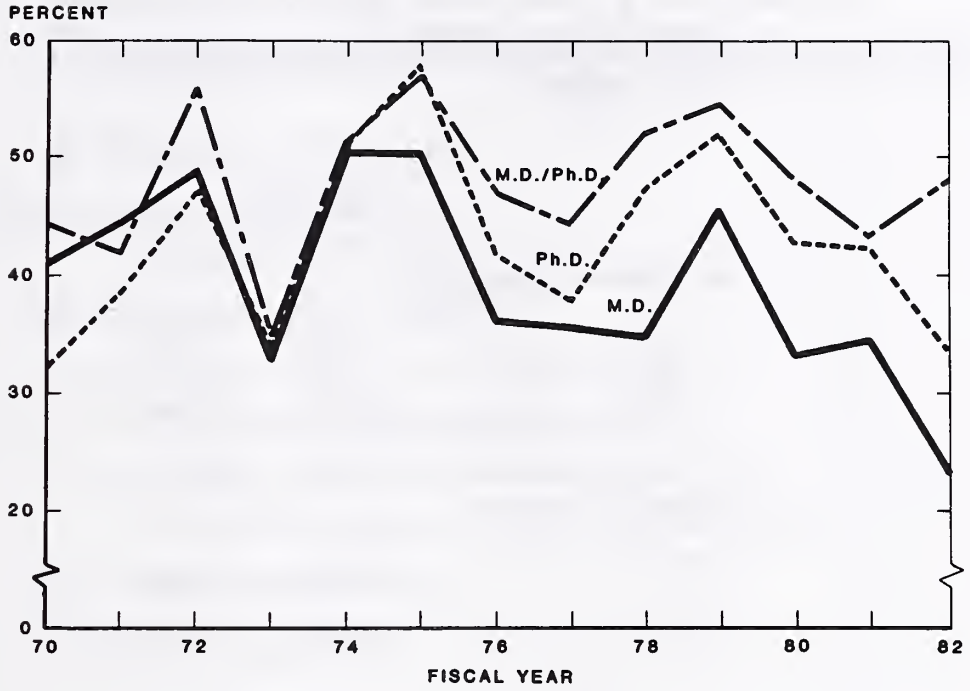


*AVERAGE INTERVAL OF 11 YEARS BETWEEN MEDICAL SCHOOL GRADUATION AND START OF FIRST GRANT.

APPROVAL, AWARD, AND SUCCESS RATES FOR
COMPETING R01 APPLICATIONS, 1974-82

Fiscal year	Approval rate		Award rate		Success rate	
	M.D.	Ph.D.	M.D.	Ph.D.	M.D.	Ph.D.
1974	72%	76%	60%	56%	43%	43%
1975	72	76	60	60	43	46
1976	68	73	50	46	34	34
1977	71	75	41	37	29	28
1978	74	79	45	45	33	36
1979	76	78	50	52	38	40
1980	76	80	42	42	32	33
1981	80	83	40	38	32	32
1982	83	85	34	34	29	29

SUCCESS OF NEW R01 APPLICANTS BY TYPE OF DEGREE



Competing R01 Applications 1976-1981

	Number Reviewed	Recommended	Award Rate	Success Rate
No Human Subjects:				
— M.D.	10,552	73%	42%	31%
— Ph.D.	40,815	74%	40%	30%
Human Subjects:				
— M.D.	12,166	64%	39%	25%
— Ph.D.	12,078	61%	38%	23%

Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

- Research Problem:
  - — Hypothesis (47%)
  - — Significance (30%)
- Experimental Design:
  - — Study Group or Controls (40%)
  - — Technical Methodology (66%)
  - — Data Collection Procedures (41%)
  - — Data Management and Analysis (31%)
- Investigator (17%)
- Resources (4%)

AVERAGE SUCCESS RATES ON NIH COMPETING
RESEARCH GRANT APPLICATIONS

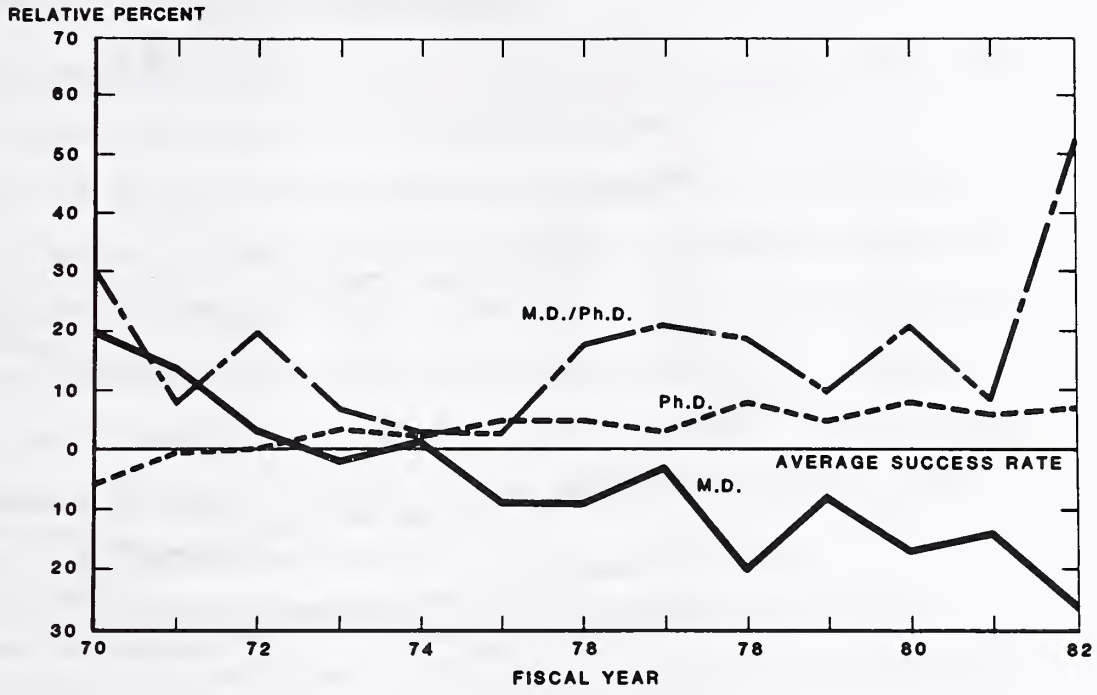
By Doctoral Degree and NIH/PHS Training Support*
FY 1967-78

Doctoral degree	Success rates	
	With training support	Without training support
M.D. or equivalent	36.5%**	25.0%**
Ph.D. or equivalent	37.9**	27.1**
Professional & academic (e.g., M.D./Ph.D.)	40.4	29.4
Other professional doctorates	41.7	27.6

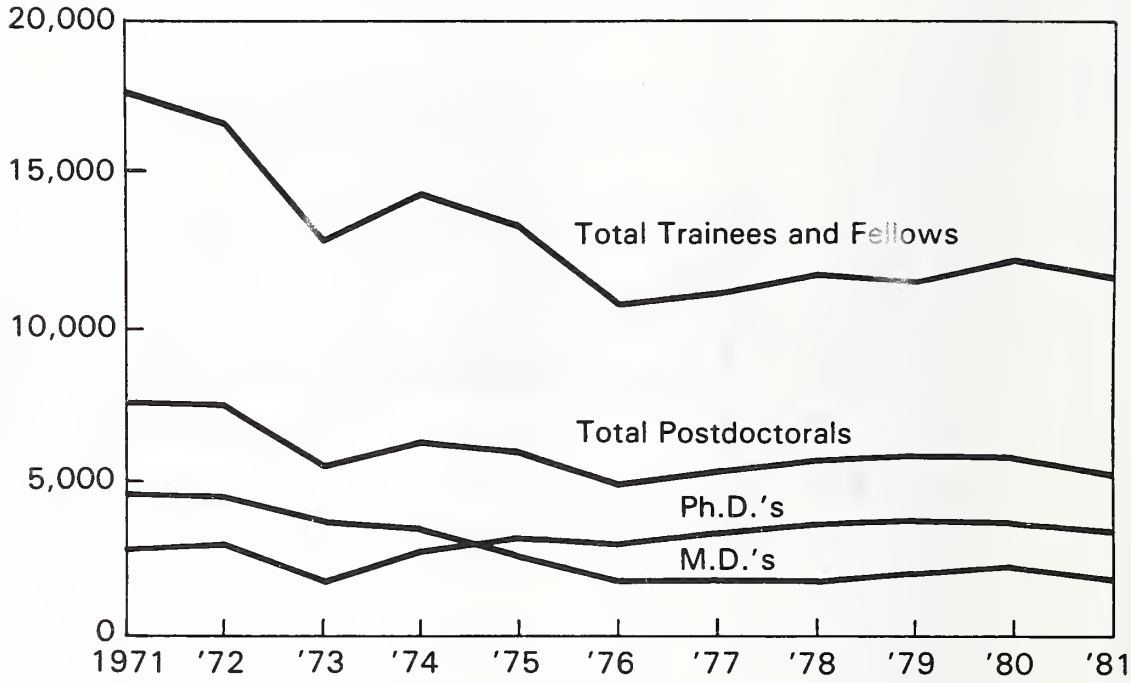
*Based on five percent random sample of NIH Grant Applicant Summary File, which includes R, P, M, and S grants. Success rate is the ratio of funded competing research grant applications to all such applications multiplied by 100.

**Significantly different at <.01 level.

SUCCESS RATES OF NEW M.D., Ph.D., AND M.D./Ph.D. APPLICANTS COMPARED WITH AVERAGE SUCCESS RATES OF ALL NEW R01 APPLICANTS IN THE SAME YEAR



TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81



REMARKS*

by

James B. Wyngaarden, M.D.**

Madame Secretary, Dr. Brandt, Dr. Williams, Mrs. Williams, Mary, other members of the Williams family, and distinguished guests.

Only a few days after being sworn in as NIH Director in April 1982, I was on my way downtown to a meeting with Ed Brandt when the car telephone rang. It was Secretary Schweiker. I'm not sure one ever gets accustomed to being called by a Cabinet member--I certainly wasn't at that time--so I have a vivid memory of the conversation. It was short and to the point. His first words were, "How are you getting along in filling all those Institute Director vacancies?" We had seven at the time.

Happily, Dr. Williams agreed to join us just a day or two before Secretary Schweiker's departure last February and I was able to send word to him that "all those vacancies" had been filled.

In the past year, we have been successful in finding and appointing extremely well-qualified replacements for seven Institute and Division Directors and two Deputy Directors. I mention these actions to make a related point. In every instance where there was a vacancy, there was a person carrying the somewhat thankless responsibility of an acting directorship--and we owe them a debt of gratitude. Today I wish to express special appreciation to Bob Ringler who has served so well as Acting Director of the National Institute on Aging.

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* Swearing-In Ceremony of Dr. T. Franklin Williams as Director, National Institute on Aging, Wilson Hall, July 5, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

I think everyone concerned recognized that it would be a formidable task to find a worthy successor to the charter Director of NIA, Dr. Robert Butler. I am delighted to say that we have been highly successful.

Dr. T. Franklin Williams comes to us from a distinguished institution where he has achieved international recognition in the field of geriatrics. He brings to his leadership role in the Institute on Aging rich experience as a scientist, educator, and clinician. We are fortunate, indeed, to have a man of his proven abilities to head one of NIH's most important and diversified programs. And I am personally gratified to be able to welcome a friend of 30 years (and fellow North Carolinian) to this post.

Dr. Williams, I believe the presence of Secretary Heckler, Assistant Secretary for Health Brandt, and the other officials at this ceremony conveys the high regard in which you and the program you will head are held in the Department of Health and Human Services. In addition, I wish to add my personal welcome to you and your family as members of the NIH community.

Welcoming Remarks*

by

James B. Wyngaarden, M.D.**

I am pleased to be among the first to welcome you to the Clinical Center and the National Institutes of Health.

It seems especially appropriate that we are meeting here in the amphitheater of this handsome Ambulatory Care Research Facility. Less than two years ago, the new facility and the original building were rechristened the Warren Grant Magnuson Clinical Center. The opening of this remarkable building and modernization of the old symbolize the commitment, the challenge, and the continuity of medical research. The additional clinical and laboratory space and the expanded capacity for patient care give us an opportunity to explore a wholly new area involving ambulatory care research.

While the hospital and laboratories provide the means for research, the professionals who work here are the lifeblood of the institution. And you, as Medical Staff Fellows, are a necessary and integral part of our research community. You are a select group--youthful, energetic, enthusiastic, creative, and talented--and we welcome you.

You will soon be taking on the major responsibilities of patient care. As primary physicians you will be responsible for treatment, for managing complications should they arise, and for carrying out the protocols under direction of an established investigator.

Here at the Clinical Center you will very likely be much more heavily involved in biomedical research. As you know, it is a rigorous and demanding

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*Presented at the Orientation of Medical Staff Fellows, July 12, 1983, ACRF Amphitheater

**Director, National Institutes of Health, Bethesda, Maryland

pursuit that requires discipline and hard work, but it offers excitement and intellectual challenge. This campus and this hospital will be your laboratory and work place.

Many of you will devote your time to research in the biomedical sciences, learning research methods and design, and engaging in the logical pursuit of a scientific problem and the critical interpretation of results. Some of you will be participating as dental staff fellows treating patients in the Dental Clinic.

In the laboratory, recombinant DNA technology has opened doors at practically every level of medical research. A particular wave of excitement attaches to research on oncogenes, their identification, the search for gene products, and the relation to known growth factors. This new method has also opened up unanticipated opportunities to improve old vaccines and develop new ones, and to manufacture biologically active substances, such as hormones, two of which--human growth hormone and insulin--are ready for clinical testing.

The powerful new tool of hybridoma technology is already widely used in science and medicine but its full potential is as yet hardly comprehended. The exquisitely specific antibodies produced by fusing two types of antibody-producing cells should facilitate the development of vaccines, improve diagnostic tests, enhance the immunotherapy of infectious diseases, and provide powerful tools for the diagnosis and treatment of cancer and other diseases. Hybridomas open up enormous possibilities in basic and clinical research.

Clinical investigation is a vital segment in the progression from basic research to prevention and treatment of disease, and is of fundamental importance to NIH. There is much to be done in clinical research, and we have the tools, the space, and the people.

You are here at a particularly interesting and exciting juncture in medical research--a time when powerful and versatile techniques are available that can yield information on molecular structure and metabolic processes.

New means of non-invasive diagnostic testing and refinements in treatment techniques are making it possible to carry out an increasing proportion of clinical care and research on an outpatient basis. CAT scanning spares the patient many of the invasive types of diagnostic procedures that had been necessary previously. PET--positron emission tomography--will allow us to follow the brain's metabolism and function in finer detail than was hitherto possible. NMR--nuclear magnetic resonance--may be the most extraordinary and sophisticated tool of all. It promises to be the window through which we will be able to see molecular structure and metabolic processes in previously inaccessible parts of the body.

We are challenged by the unprecedented rise of a new disease entity, acquired immune deficiency syndrome (AIDS), on which NIH is placing a very high priority in its intramural as well as extramural program. We know much more about AIDS than we did two years ago--about the characteristics of those at risk, about the probable mode of transmission, and about the derangement of the immune function in these patients--but we still have a long way to go in identifying the causative organism and possible therapy.

Many of you have chosen to work in the area of cardiovascular diseases. During the last 20 years, important advances in the treatment of myocardial infarction have gradually become standard clinical practice in hospitals throughout the world. The death rate for patients suffering MI has gone down, due to prompt expert prehospital coronary care, more accurate diagnosis, and

more effective treatment, to which NIH scientists have made important contributions.

However, there is much to be done. New drugs have recently been developed for reducing the size of the thrombus within the coronary vessel. They are now being testing to determine whether they will lessen muscle damage and reduce the death rate. Other approaches to limiting the size of the damaged zone include the use of new drugs to reduce the oxygen needs of the endangered area, to improve blood flow through accessory coronary blood vessels, or to improve diffusion of metabolic fuels to the damaged zone. Clinical studies are now being conducted to determine whether these drugs can indeed improve heart function and protect borderline areas of cardiac injury.

I could go on outlining the possibilities for research here at the NIH, but you will soon be involved in your own fast-paced, learning process and will begin your exploration of the research universe.

The rapid development of science makes it imperative that there be a continuing flow of new people educated and trained in the most modern concepts and techniques of science. To assure that scientists are able to recognize the potential clinical value of research findings, the number of medically trained individuals in the research pool must be continually replenished. The Medical Staff Fellowship Program offers young physicians and dentists this opportunity.

Since the program began in 1958 with the appointment of 60 Medical Staff Fellows, then called Clinical Associates, it has grown steadily. It reached its peak in the period between 1965 to 1970 when the initiatiion of the Commissioned Officers Residency Deferment Program (CORD) allowed deferment of military service if a physician or dentist entered the Associate Program here at NIH. During those five years, NIH received more than 1,000 applications

annually and from 166 to 226 appointments were made each year. In 1970 the CORD program was discontinued and the number of applicants dropped. In 1971 there were only 52 candidates selected. Since that time there has been a steady increase of applications for the Medical Staff Fellow appointments, as they are now called. This year there were 350 applicants, and 85 were selected for the 1984-85 program.

One of the striking features of the Medical Staff Fellowship Program is that it offers an exciting and stimulating medical milieu in which free-ranging scientific inquiry in a setting devoted to the study of human disease provides a vigorous incentive to remain in the field. Many choose to remain at NIH for lifetime careers of fruitful research. As you progress through your training experience here, you will note that many of the senior people, some of them your preceptors, were themselves Clinical Associates. At NCI. Dr. Bruce Chabner, Director of the Division of Cancer Treatment, came here as a Clinical Associate. Dr. Robert Young, Chief of the Medicine Branch, was an Associate in 1967 and worked in the laboratory of Dr. Vincent DeVita, now the NCI Director. Dr. Philip Pizzo, Chief of the Pediatric Oncology Branch, came in 1973 as a pediatric fellow. He worked on Epstein-Barr virus studies and then began work on the infectious complications of cancer patients, which continues today. In the NHLBI, Dr. Bryan Brewer and Dr. Arthur Nienhuis were Associates. Dr. Steve Epstein came here in 1963 as an Associate and his first project was in the NHLBI exercise laboratory. Dr. Jesse Roth of NIADDK, noted for his research on diabetes and insulin receptors, began as a Clinical Associate in 1963. And I could name many, many more.

So you can see that the Medical Staff Fellows provide much of the impetus to the research conducted here. Whether you choose to stay here as medical

investigators or move to another medical center in this country or abroad, you will influence the course of medical research in the future, and your experience at NIH will have a profound influence upon you.

INTRODUCTION OF
Dr. John B. Slaughter*
by
James B. Wyngaarden, M.D.**
NIH Black Cultural Committee Summer Program***

THANK YOU, MR. LASTER.

I WISH TO CONGRATULATE THE BLACK CULTURAL COMMITTEE FOR PLANNING THIS 1983 PROGRAM AND ESPECIALLY FOR ITS SELECTION OF DR. JOHN BROOKS SLAUGHTER AS TODAY'S SPEAKER.

DR. SLAUGHTER, BY ANY DEFINITION, IS ONE OF AMERICA'S LEADING SCIENTISTS AND EDUCATORS. HIS VERY ACTIVE AND PRODUCTIVE CAREER STANDS AS AN EXAMPLE FOR ALL YOUNG PEOPLE. BUT HE IS MORE THAN AN EXAMPLE. DR. SLAUGHTER HAS BEEN ACTIVE IN EFFORTS TO ENCOURAGE MINORITIES TO PURSUE CAREERS IN SCIENCE AND ENGINEERING AND HAS PLAYED A STRONG ROLE IN URGING EDUCATIONAL INSTITUTIONS, INDUSTRY, AND GOVERNMENT TO TAKE MORE AGGRESSIVE STEPS TO IMPROVE OPPORTUNITIES FOR MINORITIES IN THOSE FIELDS.

A NATIVE OF TOPEKA, KANSAS, DR. SLAUGHTER EARNED A BACHELOR OF SCIENCE DEGREE IN ELECTRICAL ENGINEERING AT KANSAS STATE UNIVERSITY IN 1956, A MASTER OF SCIENCE AT UCLA IN 1961, AND A DOCTOR OF PHILOSOPHY DEGREE IN ENGINEERING PHYSICS AT THE UNIVERSITY OF CALIFORNIA, SAN DIEGO, IN 1971, WHILE SERVING IN VARIOUS LEADERSHIP POSITIONS IN THE NAVAL ELECTRONICS LABORATORY CENTER IN SAN DIEGO. IN 1975, HE JOINED THE UNIVERSITY OF WASHINGTON, SEATTLE, AS DIRECTOR OF THE APPLIED PHYSICS LABORATORY AND PROFESSOR OF ELECTRICAL ENGINEERING. IN 1977, HE WAS NAMED ASSISTANT DIRECTOR OF THE NATIONAL SCIENCE FOUNDATION FOR ASTRONOMICAL, ATMOSPHERIC, EARTH AND OCEAN SCIENCES, RESPONSIBLE FOR FUNDING AND ADMINISTERING A NUMBER OF MAJOR NATIONAL RESEARCH LABORATORIES. HE RETURNED TO ACADEMIA IN 1979 AS ACADEMIC VICE PRESIDENT AND PROVOST OF WASHINGTON STATE UNIVERSITY--BUT IN MID-1980, PRESIDENT CARTER ASKED HIM TO RETURN TO WASHINGTON AS DIRECTOR OF THE NATIONAL SCIENCE FOUNDATION WHERE FOR TWO YEARS HE ADMINISTERED THAT AGENCY'S WIDE RANGING PROGRAMS IN SCIENCE, ENGINEEERING, AND TECHNOLOGY.

THEN IN NOVEMBER 1982, DR. SLAUGHTER BECAME THE CHANCELLOR OF THE UNIVERSITY OF MARYLAND'S COLLEGE PARK CAMPUS. AS CHANCELLOR, HE IS THE CHIEF ACADEMIC OFFICER OF THE MAJOR CAMPUS OF THE UNIVERSITY OF MARYLAND, THE SEVENTH LARGEST CAMPUS IN THE UNITED STATES.

FROM THIS RICH BACKGROUND OF EXPERIENCE AND ACCOMPLISHMENT, DR. SLAUGHTER WILL SHARE WITH US HIS THOUGHTS ON "SCIENCE AND EDUCATION: HOPE FOR MANKIND."

DR. SLAUGHTER:

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* Chancellor of University of Maryland's College Park Campus
** Director, National Institutes of Health, Bethesda, MD
*** Masur Auditorium, Warren Grant Magnuson Clinical Center, July 15, 1983

INTRODUCTORY REMARKS for SECRETARY HECKLER*

by

James B. Wyngaarden, M.D.**

I should like to introduce those persons on the dais. Starting on my extreme right is Dr. James F. Dickson, Senior Advisor for Environmental Affairs of the Public Health Service. Next, Mr. George Siguler, Chief of Staff, Office of the Secretary. And next, Dr. Edward N. Brandt, Assistant Secretary for Health. On my immediate right is Secretary Heckler.

Madame Secretary, we are deeply honored with your visit to the NIH campus today. On behalf of the NIH family of <u>your</u> employees, I extend a most cordial welcome.

Secretary Heckler was born in Flushing, New York. A graduate of Boston College Law School (only woman), she was admitted to both the Massachusetts Bar and the United States Supreme Court Bar. And since graduation she has had a distinguished career as an attorney.

Representing the people of Massachusetts, Secretary Heckler served in the United States Congress for eight terms -- a total of 16 years. And during those years in the Congress she demonstrated, repeatedly, her concern about the welfare of our citizens.

As Secretary of Health and Human Services (150 thousand employees, $274 billion budget), she continues to show her concern for the women of America, the aged, our minorities, the less fortunate, and the sick. She has shown a commitment to our goals of contributing to the health and well-being of the people of this country.

Today, we have been privileged to show her some of the resources that she has available to prevent and combat disease -- to provide for better health for all Americans, and mankind.

It is with great pleasure that I present to you the Secretary of Health and Human Services, the Honorable Margaret M. Heckler.

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* On her first Official Visit to NIH on July 19, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

WELCOMING REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

FIRST -- I WILL STATE THE OBVIOUS -- YOU ARE WELCOME INDEED TO THIS CONFERENCE. IT IS MY HOPE THAT IT IS EQUALLY OBVIOUS TO YOU HOW GRATEFUL WE ARE TO EACH OF YOU FOR DEDICATING THE BETTER PART OF A WEEK TO THE SUBSTANTIAL AGENDA THAT WE BEGIN NOW TO ADDRESS. I CONGRATULATE DR. JAMES KLINENBERG, DR. LARRY SHULMAN, DR. LESTER SALANS AND THE OTHERS WHO HAVE PLANNED THIS CONFERENCE AND THE STRUCTURE THEY HAVE DESIGNED FOR CONDUCTING IT.

THE ASSEMBLY OF SUCH AN ARRAY OF SCIENTIFIC TALENT AND CONCERNED LEADERS IS AN EVENT IN ITSELF. BECAUSE THE SUBJECT IS ARTHRITIS AND RELATED RHEUMATIC DISEASES, OUR CONSIDERATIONS ARE OF INTEREST AND CONCERN TO ONE OUT OF SEVEN AMERICANS--35 MILLION PEOPLE--WHO HAVE SOME FORM OF ARTHRITIS.

AND WHEN THE CENTRAL THEME IS PREVENTION OF MAJOR FORMS OF THE NATION'S LEADING CRIPPLER, THE CONFERENCE TAKES ON AN ALL-IMPORTANT ADDITIONAL DIMENSION--THE FUTURE.

THIS IS THE LAST AUDIENCE THAT NEEDS TO BE TOLD OF THE DIFFICULTY OF THE ISSUES THAT HAVE BEEN PRESENTED. THE FACT THAT IT IS THE FIRST TIME SUCH A CONFERENCE HAS BEEN HELD ON THE PREVENTION OF RHEUMATIC DISEASES IS A REMINDER OF THE STUBBORN NATURE OF THE COMPLEX OF PROBLEMS TO BE DISCUSSED, BUT MORE THAN THAT, IT IS AN INVIGORATING CHALLENGE TO CREATIVE THINKING.

I ALSO VIEW THIS CONFERENCE AS ILLUSTRATING A BASIC PRINCIPLE OF THE NATIONAL INSTITUTES OF HEALTH--ITS RELIANCE UPON THE ADVICE AND COOPERATION OF THE NATION'S ABLEST LEADERS CONCERNED WITH HEALTH RESEARCH AND ITS APPLICATION.

IN ADDITION TO THE MEMBERS OF THE NATIONAL ARTHRITIS ADVISORY BOARD AND MEMBERS OF THE STAFF OF THE NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES, THE LIST OF PARTICIPANTS IN THIS CONFERENCE

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* National Arthritis Advisory Board's Prevention Conference on Arthritis, Airlie House, Warrenton, Virginia, July 19-22, 1983

**Director, National Institutes of Health, Bethesda, MD

INCLUDES EXPERTS FROM THE BIOMEDICAL RESEARCH COMMUNITY AND RELATED HEALTH FIELDS, AS WELL AS EXPERTS FROM INDUSTRY AND PRIVATE VOLUNTARY AGENCIES.

THE ANNOUNCED GOALS OF THIS CONFERENCE ARE DEMANDING INDEED--TO IDENTIFY CURRENT AND PROSPECTIVE OPPORTUNITIES FOR EFFECTIVE PREVENTION OF MAJOR RHEUMATIC DISEASES AND TO DEVELOP STRATEGIES FOR IMPLEMENTING SUCH INTERVENTION. I AM CONFIDENT, HOWEVER, THAT THROUGH SHARING OF INSIGHTS AND INFORMATION AND IN THE GIVE AND TAKE OF YOUR WORKING GROUPS, NEW PATHS WILL BE FOUND FOR EXPLORATION.

WHAT WILL TAKE PLACE HERE IS THE KIND OF ACTIVITY THAT REPRESENTS ONE OF THE PRIME PURPOSES OF THE NIH. THE AGENCY IS UNIQUELY QUALIFIED TO ACT AS A CONVENER AND PARTICIPANT IN SURVEYING AN IMPORTANT AREA WHERE RESEARCH IS NEEDED--TO FOSTER THE DEVELOPMENT OF NEW IDEAS FOR THE SOLUTION OF OLD PROBLEMS AND ULTIMATELY TO PROVIDE SUPPORT FOR RESEARCH BASED ON SUCH IDEAS.

I CA T RESIST THE PERSONAL COMMENT THAT IT IS REFRESHING TO TAKE PART IN A CONFERENC DEVOTED SPECIFICALLY TO A SCIENTIFIC CHALLENGE AND ESPECIALLY IN A GENERAL AREA THAT HAS HELD MY OWN RESEARCH INTEREST FOR YEARS. I FIND THE JOB OF DIRECTING THE NIH TO BE FUN--MOST OF THE TIME--BUT I CONFESS THAT ENGAGING THE PUZZLES AND ENIGMAS OF SCIENCE IS EVEN MORE INTERESTING THAN CONFRONTING THE ISSUES INVOLVED IN THE ORGANIZATION AND SUPPORT OF SCIENCE.

THIS OCCASION GIVES ME AN OPPORTUNITY TO EXPRESS TO A MOST IMPORTANT AUDIENCE MY APPRECIATION AND ADMIRATION FOR THE WORK OF THE MEMBERS AND STAFF OF THE NATIONAL ARTHRITIS ADVISORY BOARD. DR. KLINENBERG, YOU AND YOUR COLLEAGUES ARE DISCHARGING ABLY THE LEADERSHIP RESPONSIBILITY GIVEN TO THE BOARD BY THE NATIONAL ARTHRITIS ACT OF 1974. THIS CONFERENCE IS BUT AN EXAMPLE OF THE INITIATIVES YOU HAVE TAKEN. THE FACT THAT YOU HAVE BEEN SUCCESSFUL IN BRINGING TOGETHER SUCH AN ARRAY OF TALENT IS AN EXPRESSION OF THE RESPECT IN WHICH THE BOARD'S EFFORTS ARE HELD IN THE SCIENTIFIC AND VOLUNTARY COMMUNITIES.

YOUR EXCELLENT ANNUAL REPORT FOR 1983 IS A CLEAR STATEMENT AND A CALL TO ACTION. I HOPE EVERY PARTICIPANT IN THIS CONFERENCE IS WELL ACQUAINTED WITH IT.

PERHAPS IN THE NEXT FEW DAYS WE CAN FIND NEW CLUES THAT WILL HELP US WEND OUR WAY THROUGH MORE OF THE TROUBLESOME PASSAGES IN THE EXCEEDINGLY COMPLEX MAZE THAT THE RHEUMATIC DISEASES REPRESENT.

IF SO, OUR TIME AND EFFORT WILL HAVE BEEN MORE THAN JUSTIFIED. I SHARE THE BOARD'S OPTIMISM, AS EXPRESSED IN ITS REPORT, THAT THE INVESTMENT OF AMPLE

RESOURCES, FINANCIAL AND CREATIVE, WILL "IN THE LONG RUN, RESULT IN A BETTER UNDERSTANDING OF THE CAUSES OF ARTHRITIS AND IMPROVED TREATMENT TECHNIQUES, BETTER CARE FOR PATIENTS, AND IN THE ULTIMATE ERADICATION OF RHEUMATIC DISEASES AND THEIR TRAGIC CONSEQUENCES."

INTRODUCTORY REMARKS*

by

James B. Wyngaarden, M.D.**

Thank you very much. Let me add my words of welcome to all of you in this Conference. Dr. Bick spoke on behalf of the National Institute of Neurological and Communicative Disorders and Stroke. I would like to extend a welcome on behalf of the entire NIH community.

This is a significant conference. It is worth looking back to the origins of the field in which you are interested and in which so many of us have been working. As you know, the concept of inborn errors was originated in 1908 by Sir Archibald Garrod. It took forty years before that concept was confirmed biochemically when Gibson in 1948 demonstrated an absence of NADH dependent methemoglobin reductase in recessive methemoglobinemia. We are now 35 years past that event, and the progress during this time has been remarkable indeed. In fact, there are now about 300 disorders in which the precise biochemical defect has been defined, neglecting the extensive polymorphism of some of these. The last catalog that Victor McKusick published in 1982 lists 934 autosomal dominant conditions, 588 autosomal recessive conditions, and 118 x-linked conditions for which loci are well-established. There is an equal number for which loci have not yet been formally established but which are presumed to exist on sound evidence, giving us at least 3368 discrete inherited diseases defined so far.

We have moved far past the descriptive phase, of course. Extensive heterogeneity is now known to exist for many of these conditions. Gene mapping is now well upon us and over 350 specific genes have been mapped to a precise chromosome, in most of these to a specific location on that chromosome. We have also moved far past mapping, and precise molecular defects have been defined in many conditions at the level of the genes. Specific nucleotide replacement or deletion or insertion in now well-defined for a substantial number of these, including some in the field in which you are working. I thought it might be interesting to mention just one of these conditions, thalassemia, to which DNA recombinant research has contributed in a special way. In that disorder we have the following precise defects already defined: single base changes in a promoter, premature chain termination mutations at two sites, frameshift mutation at five sites, splice junction mutations at four sites, intron mutations in three positions, and exon mutations affecting RNA processing at two positions. Others will follow very shortly, in fact they already have in The Lesch-Nyhan syndrome where there are five separate mutations now precisely defined; citrillinemia is another example.

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* Presented at The Molecular Basis of Lysosomal Storage Diseases Conference on September 12, 1983, at the Bethesda Holiday Inn.

** Director, National Institutes of Health, Bethesda, Maryland.

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The study of lysosomal disorders has made enormous contributions to this field, in leading to chemical identification of a number of new storage substances, in providing new insights into the biochemistry of muclopoly-saccaridoses and other disorders, new insights into the processing and storage of biological materials, identification of new enzymes, identification of new defects of these enzymes in specific disorders, and new approaches to therapy such as enzyme replacement, perhaps shortly gene replacement.

We look forward to very rapid progress in the near future. The power of these new tools, these new techniques, is awesome. The pace is extremely rapid. It is an excellent idea to pause from time to time to take stock of where we are. You are doing that in the next three days, and then you will depart to take one more step into the future.

I wish you well, wish you success in this very exciting conference. I hope I can attend a little bit of it, but as Dr. Bick mentioned, this is a lively time in town and we have some budget matters to work on. So, I am certain that you will be tolerant of my absence, if you know that your funding depends on it. Thank you very much for this opportunity.

REMARKS*

by

James B. Wyngaarden, M.D.**

Mr. Chairman, let me say at the outset how pleased I am to be able to attend this meeting of representatives of the Committee on Medical and Public Health Research of the Commission of the European Communities and to report on the state of programs of the National Institutes of Health (NIH). As you know, this is my first opportunity to attend a meeting of the CEC.

The NIH continues to accord a high priority to international cooperation in biomedical research. Also, we anticipate no change in our long-standing policy of supporting excellent research applications received from scientists outside the United States, and particularly when there is some unique aspect to the research proposal that extends beyond similar projects that might be conducted within our own country. During fiscal year 1982 we supported about $62 million worth of research and related activities involving foreign countries. About half of this amount supported research grants and contracts outside the United States or American scientists abroad and related travel expenses.

Today I will spend a few minutes talking about NIH programs and budget, and then briefly summarize NIH involvement in an issue that is a matter of great concern within the U.S. and one that is becoming an international problem--namely, the issue of Acquired Immunodeficiency Syndrome (AIDS). At the risk of repeating statistics you have already heard, I would like to take a look at how the NIH budget has changed during the last 25 years and the impact of these changes on NIH programs. As you know, NIH's main program growth came during the period of 1955-1968 when Dr. James Shannon was Director of the NIH. The budget when he entered office was $82 million, and when he left was over $1 billion. Since that time, growth has been much more modest. Between 1972 and 1983 there has been a 15 percent increase in constant dollars, but the growth of indirect costs during this period almost exactly consumed this increment so that the funds available to support the direct costs of research are essentially the same in 1983 as in 1972. The high water mark of the NIH budget was reached in 1979. The budget then fell by 12 percent in purchasing power between 1979 and 1982 but rose by 4 percent in 1983 for a net decrease of 8 percent. In short, the NIH budget has been essentially in a steady state for more than a decade. At the same time I should point out that NIH has fared better than many other agencies during this period of economic constraint, because of the high priority given this endeavor by both the Administration and the Congress.

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* Presented at the meeting of the Committee on Medical and Public Health Research of the Commission of the European Communities, Brussels, Belgium, September 15, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

A few other statistics may also be of interest. About 12 percent of our budget is spent in research conducted intramurally at the NIH, chiefly in Bethesda. Eighty-one percent of our budget is spent extramurally, chiefly in academic health centers and other institutions of higher education. Overall we classify 54 percent of the research that we support as basic, 37 percent as mission-oriented, and 10 percent as developmental.

Historically, we have accommodated to the relatively constant budget of the past decade by shifting funds from other NIH mechanisms so as to support as many excellent investigator-initiated research proposals as possible. These changes began in 1974, but were not articulated as a stabilization policy until fiscal year 1980 when we asked the U.S. Congress for sufficient funds to support a minimum of 5,000 new and competing research grants and 10,000 trainees. In 1974 about 63 percent of our extramural support was in the category of research grants; this year that fraction is 83 percent. The shift came at the expense of support for contracts, centers, clinical trials, research instrumentation, and facilities. Since our fundamental mission is the improvement of health and well-being, we must also emphasize prevention of disease and disability and make a special effort to see that scientific discoveries are transferred to medical practice as quickly as possible. As a consequence, we have continued to place particular emphasis upon research that is prevention oriented and upon technology transfer.

The stabilization policy has enabled us to dampen large fluctuations in support of new and competing research awards. In 1981 we supported 5,140 grants; in 1982, 5,027 grants; and the 1983 budget projects support of 4,914 new and competing grants awards out of a research grant portfolio of about 16,357. The 1983 budget will also support 9,969 research trainees. New scientists are entering the biomedical research enterprise at rates consistent with historic figures. About 50 percent of all new and competing awards goes to first-time applicants, and about 10 percent of our entire grant portfolio of over 16,000 awards goes to first-time applicants. This is a result of their ability to compete, not because of any protectionist policy for new applicants.

The President's proposed fiscal year 1984 budget is $4.077 million, representing a 1.8 percent increase over 1983. The Administration has instructed us to support 5,000 new and competing project grants and some 9,000 research trainees. In order to meet these goals we have had to make some rather drastic cutbacks in support of specialized centers and biomedical research support grants which contain flexible funds for use of research-intensive institutions. In our budgetary hearings before the Congress, which have just been concluded, there was strong indication in both the House of Representatives and the Senate that the Congress might add funds to the President's budget to make these cutbacks unnecessary.

We may have reached the limit of utility of the stabilization policy in its present form. Many Institute Directors feel that further shifts of funds into the research grant category would seriously limit their ability to meet other program goals and to maintain program balance. This year we are involving the Director's Advisory Committee in a review of the impact of our stabilization policy on all of NIH, and particularly on the extramural program. It is likely that the concept of stabilization will be modified, perhaps to set an upper limit of the percentage of our extramural budget that will be assigned to research grants.

Another continuing issue of concern is the training of sufficient numbers of investigators to maintain the vitality of research. Although there is currently an adequate supply of scientists in most fields, the proportion of physicians involved in biomedical research is diminishing. The success rate among applicants for grants has historically been about the same for investigators with combined M.D./Ph.D. degrees, Ph.D. degrees, or M.D. degrees. But since about 1974, there has been a progressive divergence with M.D./Ph.D. degree applicants competing most successfully, followed by Ph.D. applicants--both of which are well above the average--and then by M.D. applicants, whose success rate is steadily declining and is now far below the first two categories.

There are also fewer physicians interested in training in biomedical research. Of the 2,800 positions that the National Academy of Sciences recommends be devoted to clinical research training, only 1,900 are filled by M.D. trainees. The major barriers to attracting physicians include the income possibilities of private practice, the length of subspecialty training programs, the lack of research experience during medical school training, the increasing complexity of science which in turn leads to a need for longer research training, the widening gap between laboratory and bedside, the educational debtload incurred by physicians which now averages $19,000 at the time of graduation, and the relatively low level of research training stipends which now average some $6,000 less than the equivalent house staff position in a hospital. There is also the apparent instability of federal commitment to research support, and the intense competition for research funding that physicians in training observe among the faculty of the medical schools.

In recognition of the increasing complexity and professionalization of biomedical research, we are instituting a new type of physician scientist training program which will provide support for 5 years of combined full-time research training and initial faculty support, with stipends well above the residency levels. The award will also include $10,000 to $20,000 per year for the costs of research. This training program will enable young physicians to return to basic science departments for an initial period of two to three years and will provide some initial salary support for the first few years of an academic appointment. The program will start on a rather small scale, initially perhaps supporting about 400 trainees per year. We are also offering several programs of shorter term support at the medical student level designed to provide research experiences during off-quarters or elective years of the medical curriculum. We are hopeful that the combination of earlier introduction to research and a more prolonged period of support for more intensive training in basic biomedical science will make a contribution toward repairing the perceived deficit in physician investigators in biomedical science.

Finally, I would like to comment on a high priority research area of international interest, the Acquired Immunodeficiency Syndrome (AIDS). When the AIDS problem was recognized in early 1981, close liaison was established among the Public Health Service agencies in the U.S. with major responsibility in this area, each emphasizing its primary mission: the Centers for Disease Control (CDC), surveillance and investigation; the Food and Drug Administration (FDA), preventive measures related to blood collection and its use; and NIH, research into fundamental causes and clinical aspects of AIDS.

Since June 1981, when CDC initiated national surveillance, more than 2,200 cases of AIDS have been reported from 41 states and the District of Columbia and 123 cases from 20 foreign countries. Of the cases in the United States, 926 deaths (40 percent) have thus far occurred. Of the 285 reported AIDS cases diagnosed before January 1, 1982, 79 percent of the patients have died. Incidence by date of diagnosis has roughly doubled every six months since the second half of 1979, and is still rising.

As you know, current epidemiologic evidence identified several groups in the United States at increased risk for developing AIDS. Most cases (75.7 percent) have been reported among sexually-active homosexual or bisexual men, primarily young (25-45) and urban. The second largest group (14.5 percent) of AIDS patients are heterosexual persons who are abusers of intravenous drugs such as heroin. A third group of AIDS patients (5 percent) is made up of Haitians, especially those who have entered the country in recent years. Other groups of AIDS patients are persons with hemophilia and no history of homosexuality, intravenous drug use, or Haitian background (0.9 percent) and those with no apparent characteristics of the other risk groups (3.9 percent).

During fiscal 1983, the NIH will spend approximately $9.5 million from its original budget on research projects specifically related to the AIDS problem. Also, Congress has recently passed a supplemental appropriation of an additional $9.5 million for NIH during the current fiscal year. These funds for highly focused and targeted research are superimposed on a very large base of support in such areas as immunoregulation, viral agents, opportunistic infections, and blood purification and storage. NIH research programs in immunosuppression and related fields, generally relevant to but not specifically targeted upon the AIDS problem, amount to about $200 million per year. There is also a potential animal model of this disorder. Two primate colonies in the United States have developed acquired immunodeficiency states, unrelated to any known cause. In both colonies, young monkeys fall prey to opportunistic infections chiefly of the gastrointestinal tract. In this respect, their illness resembles the clinical syndrome seen in Haiti somewhat more closely than that seen in the United States. In Haiti the AIDS patients tend to develop gastrointestinal candidiasis or other parasitic and bacterial enteritides, whereas in the United States opportunistic infections of the lung are more common.

Some months ago, NIH convened a meeting of biologists with expertise in the isolation of new infectious agents. It was their view that a viral etiology of AIDS was probable. Leading candidates were thought to be an animal virus, perhaps recently accommodated to man, or a new mutant of some known virus. Recent research has suggested some relationship between AIDS and T-cell leukemia virus in at least some victims. Until the etiology of AIDS is understood, it will continue to be a health threat in the United States and throughout the world. We consider it critical that the international scientific community work together in this important endeavor and urge maximum attention through your Councils to this problem.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

Good Morning:

I look forward to meeting from time to time with each of the Institute Advisory Councils to discuss major issues and problems confronting NIH to get a sense of what is of current concern to the scientific community, and to have a chance to talk to the council members.

So for all these reasons, it is a pleasure to be with you today. In fact it is a special pleasure for, as many of you know, I have deep professional roots in this part of the country, having spent most of my professional life at Duke.

This morning I would like to discuss with you four issues that have an impact on the extramural programs of the NIH and on the scientific community they serve. These are:

1. The concept of stabilization and its effect on programs of the NIH.

2. The Centers programs of the various Institutes and their utility in achieving the program goals of the Institutes.

3. The need to attract greater numbers of young physicians into careers in research.

4. The new GSA Federal Advisory Committee regulations which, among other things, would make payment of honoraria to advisory committee members the exception rather than the rule.

Stabilization

The basic concept of stabilization is a commitment by the NIH to maintaining approximately 15,000 active research individual research grants of which approximately 5,000 should be new or competing grants awarded each year.

It now appears that under current funding levels, the NIH may be approaching limits for stabilization beyond which the policy as now formulated would be counter productive. Just as there are limits to the amounts of resources that can be shifted from other program mechanisms to support the funding of research project grants without creating serious program imbalances, so are there limits to the reductions that can be made in funds awarded to support an individual research project grant without defeating the purposes for which those funds are awarded.

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*Meeting of the National Advisory Environmental Health Sciences Council, Research Triangle Park, N.C., September 19, 1983.

**Director, National Institutes of Health, Bethesda, MD.

It is against this backdrop that the stabilization concept, which has demonstrated its utility over the past several years, is being subjected to intensive scrutiny. Our examination does not signal the abandonment of the stabilization strategy but instead indicates our desire to seek modifications and refinements where necessary to achieve long-range workable solutions to issues concerning the allocation of research resources. Thoughtful examination of the factors contributing to the costs of biomedical research will be required to guide the development of future funding policies.

Centers Programs

Over the past ten or fifteen years there has been almost continuous dialogue about, and examination of, the various Institute Centers programs. Frankly, some of this examination has appeared to result in a lot of discussion and relatively little action. Part of the reason for this is that the word "Center" is used by several Institutes to describe quite dissimilar activities. In addition, there are significant differences in the percentage of extramural dollars invested in Centers in one Institute as opposed to another.

These activities, by whatever name, are important to the goals and purposes of the individual Institutes.

At the same time, both the NIH and the scientific community it serves tilt strongly toward the support of investigator-initiated research through the individual research project.

Thus, the Institute which invests a significant percentage of its resources in Centers has to assure itself that such an investment is of critical program relevance to it.

The nature of the NIEHS mission seems to demand a particularly high degree of interdisciplinary research and core support for the conduct of that research. The nine Centers supported by the NIEHS are located in some of the nation's finest Institutions and involve some of our leading scientists. To mention a few: The Center at New York University, directed by Arthur Upton; the Environmental Health Sciences Center at the University of California, headed by Bruce Ames; and the Center for the Study of the Human Environment at the University of Cincinnati, headed by Raymond R. Suskind.

Each of these and the other equally important Centers employs a multidisciplinary approach to carrying out its mission.

I would be interested in hearing your comments on the use of this mechanism of support.

The Physician Scientist

At the Director's Advisory Committee meeting last January, we had quite an extensive discussion of the need to increase the number of physicians in research. While it is clear that the Ph.D. will continue to constitute most of the pool of scientists in basic biomedical research, I do believe that there are important and continuing needs for physician scientists in this field. This is particularly true in the area of clinical medicine.

There are many vital research studies that cannot legally, or ethically, be done by other than a licensed physician because patients must be involved--research on the etiology, pathogenesis and treatment of infant respiratory diseases syndrome, for example. Another would be clinical studies of anti-coagulant and clot dissolving agents in the prevention and treatment of thromboembolic episodes. On every hand, there are important studies where physicians are absolutely necessary.

However, the trend in the past decade has been counter to this need. In 1983 there are 25 percent fewer M.D.s holding research projects than there were in 1973. In my view, this does not augur well for a vital national program in clinical research. We consider this a matter for serious attention and have initiated different measures designed to show or possibly reverse this downward trend. The newest addition to our career development award programs is a part of this effort. In mid July, the NIH announced the physician-scientist award supported by eight of the Institutes, including NIEHS.

As you know, the award is intended to encourage newly trained clinicians to develop independent research skills and experience in a fundamental science. The awards will enable physicians to undertake up to five years of phased and supervised research experience and support them in the transition from clinical training status to that of a productive investigator able to compete successfully for NIH research support.

GSA Committee Management Regulations

In recent months, the General Services Administration, which has operational responsibility for the Federal Advisory Committee Act, issued draft regulations which would have a variety of impacts. Probably the major provision is the one which would result in council and study section members no longer receiving honoraria. We have protested this draft regulation vigorously, and the Secretary has endorsed our views in her official response to the head of GSA regarding the proposed rule. A final decision on the regulation is expected before the first of November.

This morning, I have discussed a few of the issues which seem to be of broad interest to the scientific community and which are absorbing significant amounts of time of those of us involved in managing the activities of the NIH.

I would be delighted to discuss these or any other issues with you.

FOCUS ON THE HEALTH INDUSTRIES*

by

JAMES B. WYNGAARDEN, M.D.**

I HAVE NOTED WITH INTEREST THE DECISION OF YOUR PROGRAM COMMITTEE TO INVITE A REPRESENTATIVE OF THE RESEARCH COMMUNITY TO GIVE THE KEYNOTE ADDRESS FOR THIS CONFERENCE ON THE HEALTH INDUSTRY. THE TOTAL OF DOLLARS INVOLVED IN BIOMEDICAL RESEARCH AND DEVELOPMENT REPRESENTS LESS THAN THREE PERCENT OF THE NATION'S HEALTH-RELATED EXPENDITURES. BUT THE REALIZED BENEFITS AND THE POTENTIAL IMPORTANCE OF SCIENTIFIC RESEARCH IN THE HEALTH FIELD FAR EXCEED THAT RATIO. IN ADDITION, BIOMEDICAL RESEARCH HAS A CATALYTIC EFFECT UPON THE ECONOMY IN GENERAL. A RECENT STUDY CONCLUDED THAT MEDICAL RESEARCH EXPENDITURES LED TO A TENFOLD RETURN TO OUR GROSS NATIONAL PRODUCT.

NATIONAL EXPENDITURES FOR HEALTH-RELATED RESEARCH AND DEVELOPMENT IN THE UNITED STATES DURING 1983 CAME TO AN ESTIMATED TOTAL OF $10.34 BILLION. OF THIS AMOUNT, THE FEDERAL GOVERNMENT SUPPLIED 52.5 PERCENT AND INDUSTRY A LITTLE OVER 38 PERCENT. IT IS ALSO IMPORTANT TO NOTE THAT ALMOST HALF (47 PERCENT) OF THE BIOMEDICAL RESEARCH CARRIED OUT IN THIS COUNTRY WAS CONDUCTED IN ACADEMIC AND OTHER NONPROFIT INSTITUTIONS. SO, AS I ADDRESS THE SUBJECT OF CURRENT TRENDS IN BIOMEDICAL RESEARCH, I WILL DO SO LARGELY FROM THE DUAL PERSPECTIVES OF ACADEMIA AND THE FEDERAL GOVERNMENT. THIS IS ALSO A REFLECTION OF MY LONG-TIME PERSONAL COMMITMENT TO TEACHING AND RESEARCH IN AN ACADEMIC SETTING AND MY CURRENT RESPONSIBILITIES WITH THE FEDERAL GOVERNMENT'S PRINCIPAL AGENCY FOR BIOMEDICAL RESEARCH.

THE VIEW OF TECHNOLOGY AS A POSITIVE ELEMENT OF GOVERNMENT ECONOMIC POLICY ONLY EMERGED AFTER WORLD WAR II. PRESIDENT ROOSEVELT'S PROGRAMS FOR ECONOMIC RECOVERY IN THE 1930s INCLUDED NO SPECIFIC PROVISION FOR THE STIMULATION OR SUPPORT OF RESEARCH AND DEVELOPMENT, ALTHOUGH SOME PROGRAMS HAD THE EFFECT OF PROVIDING SUPPORT FOR SOME ACADEMIC RESEARCHERS. IN FACT THE DOMINANT BELIEF OF THE TIME WAS THAT TECHNOLOGY CAUSED UNEMPLOYMENT, PRECISELY THE PROBLEM THEY WERE TRYING TO CURE. IT WAS NOT UNTIL AFTER THE WAR THAT THE FEAR OF TECHNOLOGICAL UNEMPLOYMENT RECEDED AND A CURRENT VIEW OF TECHNOLOGY AS AN ECONOMIC GROWTH AGENT COULD COME TO THE FORE.

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* Keynote Address, New York Society of Security Analysts, New York, September 20, 1983.

** Director, National Institutes of Health

FOR THE PURPOSES OF OUR DISCUSSION, I WILL SKETCH BRIEFLY THE HISTORY OF THE DEVELOPMENT OF THE NATIONAL INSTITUTES OF HEALTH. SUCH A NARRATIVE NECESSARILY INCLUDES MUCH ABOUT THE DEVELOPMENT OF THE RESEARCH CAPABILITIES OF AMERICA'S ACADEMIC INSTITUTIONS AS WELL.

ALTHOUGH THE NIH TRACES ITS ROOTS TO A ONE-ROOM LABORATORY IN THE MARINE HOSPITAL ON STATEN ISLAND ESTABLISHED IN 1887 TO STUDY CHOLERA AND SIMILAR INFECTIOUS DISEASES, THE AGENCY AS IT IS KNOWN TODAY HAD ITS REAL BEGINNING IN THE YEARS IMMEDIATELY AFTER WORLD WAR II. PRIOR TO THE WAR, THE NIH HAD BEEN QUITE A SMALL FEDERAL AGENCY WITH ITS ACTIVITIES ALMOST ENTIRELY CONFINED TO ITS OWN LABORATORIES. IT WAS THROUGH THE GOVERNMENT'S WARTIME PARTNERSHIP WITH ACADEMIC INSTITUTIONS IN RESEARCH ON MILITARILY RELATED HEALTH PROBLEMS THAT THE NIH RECEIVED THE IMPETUS FOR ITS RAPID GROWTH IN THE POSTWAR YEARS. THE GROWTH OF FEDERAL SUPPORT OF BIOMEDICAL RESEARCH IN ACADEMIC INSTITUTIONS HAS BEEN SO RAPID IN THE LAST 40 YEARS THAT THIS BRANCH OF SCIENCE NOW RECEIVES ALMOST HALF OF ALL FEDERAL RESEARCH AND DEVELOPMENT FUNDS AWARDED TO UNIVERSITIES, COLLEGES, AND NONPROFIT LABORATORIES.

BUT LET ME RETURN TO FILL IN A FEW DETAILS OF NIH HISTORY. IN THE SUMMER OF 1940, THE SURGEONS GENERAL OF THE MILITARY SERVICES CALLED UPON THE NATIONAL RESEARCH COUNCIL FOR ADVICE IN MANY FIELDS OF MEDICINE AND SURGERY. THE FOLLOWING YEAR, THE COMMITTEE ON MEDICAL RESEARCH WAS ORGANIZED UNDER THE OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT TO "INITIATE AND SUPPORT SCIENTIFIC RESEARCH ON MEDICAL PROBLEMS AFFECTING THE NATIONAL DEFENSE." BY DECEMBER 1944, THE COMMITTEE HAD EXECUTED ALMOST 500 CONTRACTS FOR MEDICAL RESEARCH AT 120 DIFFERENT INSTITUTIONS. OVER 95 PERCENT OF THESE RESEARCH AGREEMENTS WERE WITH UNIVERSITIES OR TEACHING HOSPITALS. AT THE END OF THE WAR, THE EXISTING AGREEMENTS WERE ASSIGNED TO THE NATIONAL INSTITUTES OF HEALTH FOR ADMINISTRATION. IT WAS FROM THIS NUCLEUS THAT THE LARGE EXTRAMURAL COMPONENT OF THE NIH DEVELOPED.

THE POLICIES FOR POSTWAR FEDERAL SUPPORT OF HEALTH AND OTHER KINDS OF RESEARCH WERE OUTLINED BY VANNEVAR BUSH, THE PRESIDENT'S SCIENCE ADVISOR IN A REPORT WRITTEN IN 1945 AND TITLED "SCIENCE--THE ENDLESS FRONTIER." THE FLAVOR AND SUBSTANCE OF THE DOCUMENT STAND UP WELL WHEN VIEWED FROM THE PERSPECTIVE OF NEARLY 40 YEARS.

PERMIT ME TO READ A FEW SENTENCES FROM IT: "THE PUBLICLY AND PRIVATELY SUPPORTED COLLEGES, UNIVERSITIES, AND RESEARCH INSTITUTES ARE THE CENTERS OF BASIC RESEARCH. THEY ARE THE WELLSPRINGS OF KNOWLEDGE AND UNDERSTANDING. AS LONG AS THEY ARE VIGOROUS AND HEALTHY AND THEIR SCIENTISTS ARE FREE TO PURSUE THE TRUTH WHEREVER IT MAY LEAD, THERE WILL BE A FLOW OF NEW SCIENTIFIC KNOWLEDGE . . ."[1]

THEN, IN WORDS DIRECTLY PERTINENT TO TODAY'S CONFERENCE, HE WENT ON TO SAY, "WHILE ADDITIONAL PHYSICIANS, HOSPITALS, AND HEALTH PROGRAMS ARE NEEDED, THEIR FULL USEFULNESS CANNOT BE ATTAINED UNLESS WE ENLARGE OUR KNOWLEDGE OF THE HUMAN ORGANISM AND THE NATURE OF DISEASE. ANY EXTENSION OF MEDICAL FACILITIES MUST BE ACCOMPANIED BY AN EXPANSION OF MEDICAL TRAINING AND RESEARCH."[2]

IT IS INTERESTING TO NOTE THAT THE DISCOVERY OF ANTIBIOTICS AND THEIR WIDESPREAD USE DURING WORLD WAR II BECAME A COMPELLING ARGUMENT FOR FEDERAL SUPPORT OF BASIC AND APPLIED BIOMEDICAL RESEARCH AFTER THE WAR. IT WAS A MOST CONVINCING DEMONSTRATION OF THE VALUE TO THE NATION OF THE FRUITS OF BIOMEDICAL RESEARCH--A FORETASTE THAT CONVINCED THE POLICY MAKERS OF THE TIME THAT SUBSTANTIAL FEDERAL SPONSORSHIP OF SUCH RESEARCH WAS AN ESSENTIAL AND APPROPRIATE FUNCTION OF GOVERNMENT.

AND IN THE YEARS SINCE THE MID-FORTIES, THE WISDOM OF THOSE DECISIONS HAS BEEN CONFIRMED AND RECONFIRMED AS NEW GENERATIONS OF POLICY MAKERS HAVE INSISTED THAT FEDERAL EXPENDITURES FOR BIOMEDICAL RESEARCH REPRESENT A PRUDENT INVESTMENT OF PUBLIC FUNDS. JUST TO STATE THE SIZE OF THE CURRENT BUDGET OF THE NATIONAL INSTITUTES OF HEALTH--FOUR BILLION FOUR MILLION DOLLARS--IS A WAY OF SUMMARIZING THE POLICY DECISIONS AFFECTING FEDERAL SUPPORT OF BIOMEDICAL RESEARCH SINCE WORLD WAR II. THE FACT THAT FOUR-FIFTHS OF THAT BUDGET IS EXPENDED IN GRANTS AND CONTRACTS AWARDED TO OUTSIDE ORGANIZATIONS, MOSTLY ACADEMIC INSTITUTIONS, IS IN TURN AN ELOQUENT STATEMENT OF OUR RELIANCE UPON OUR NON-FEDERAL PARTNERS.

THE MANDATE OF THE NIH IS TO CONDUCT AND SUPPORT RESEARCH, BUT IN ORDER TO DO THIS, IT MUST ALSO BE CONCERNED WITH THE WELL-BEING AND STABILITY OF THE RESEARCH INSTITUTION. THE TWO ELEMENTS, SUPPORT OF RESEARCH AND THE HEALTH OF THE RESEARCH INSTITUTION, ARE INSEPARATELY LINKED ONE TO THE OTHER. TO PUT IT EVEN MORE STRONGLY, THE FEDERAL GOVERNMENT--NIH--IN CARRYING OUT ITS RESEARCH MISSION, IS IN FACT DEPENDENT UPON THE INSTITUTIONS. OUR CONCERN IS ENHANCED TODAY AS INSTITUTIONS ARE CONTENDING WITH AN ARRAY OF TROUBLESOME ISSUES: PHILANTHROPY ON THE WANE, THE DISAPPEARANCE OF CONSTRUCTION GRANTS, AND REDUCTIONS IN REIMBURSEMENT FOR PATIENT CARE.

WHEN BUSH FOCUSED ON THE UNIVERSITY AND THE ACADEMIC HEALTH CENTER AS THE PROPER ENVIRONMENTS FOR THE PURSUIT OF BIOMEDICAL SCIENCE, HE CLEARLY DID SO BECAUSE HE RECOGNIZED THAT AT THE CRUX OF THE SCIENTIFIC RESEARCH UNDERTAKING IS THE INDIVIDUAL SCIENTIST HOUSED AT THE INSTITUTION.

HE RECOGNIZED THAT APART FROM TEACHING, A PRIMARY OBLIGATION OF THE MEDICAL SCHOOLS AND UNIVERSITIES IS TO CONTINUE THE TRADITIONAL FUNCTION OF SUCH INSTITUTIONS--NAMELY TO PROVIDE THE INDIVIDUAL WORKER WITH AN OPPORTUNITY FOR A FREE STUDY OF NATURE IN THE DIRECTIONS AND BY THE METHODS SUGGESTED BY HIS OR HER INTERESTS, CURIOSITY AND IMAGINATION.

IN ADDITION TO PROVIDING A CONSTANT FLOW OF NEW, YOUNG TALENT, THE UNIVERSITY HISTORICALLY HAS AN ADDITIONAL CHARACTERISTIC WHICH MAKES IT A NATURAL ENVIRONMENT FOR RESEARCH. THAT IS THE TRADITION OF ACADEMIC FREEDOM WHICH PROTECTS THE ABILITY OF THE RESEARCHER TO FOLLOW LEADS AS HE OR SHE IS DRAWN. THIS IS A MAJOR RESPONSIBILITY OF THE INSTITUTIONS.

THE ACADEMIC HEALTH CENTER HAS MUCH TO GAIN FROM ITS RESEARCH COMPONENT. THE LINKING OF RESEARCH AND TEACHING IS VALUABLE TO BOTH ENTERPRISES. EDUCATION IS DIMINISHED IF IT DOES NOT EXPOSE STUDENTS TO COMMITTED SCHOLARS AND RESEARCHERS. MOREOVER, THE RESEARCH ENTERPRISE ALSO GAINS, FOR STUDENTS WITH FRESH IDEAS CAN OFTEN STIMULATE THEIR MENTORS IN THE EXPLORATION OF NEW AVENUES. THE HEALTH CARE COMPONENT OF THE ACADEMIC CENTER AND THE RESEARCH UNDERTAKING ALSO PROVIDE MUTUAL ENHANCEMENT. HEALTH CARE WORKERS MAY BE STIMULATED TO APPLY AS APPROPRIATE THE LATEST RESEARCH ADVANCES, AND RESEACHERS AND STUDENTS ALIKE BY VIRTUE OF THEIR EXPOSURE TO PATIENTS MAY BE MOTIVATED TOWARD SOME UNFORESEEN BUT FRUITFUL PURSUIT.

ON THE GOVERNMENT SIDE OF THIS SPONSORSHIP, ANOTHER PRINCIPLE IS VIRTUALLY SACROSANCT: THE GOVERNMENT SHOULD MAKE GRANTS THAT WOULD ALLOW COMPLETE INDEPENDENCE AND FREEDOM FOR THE SCIENTIST TO DETERMINE THE NATURE, SCOPE, AND METHODOLOGY. "SCIENTIFIC PROGRESS," BUSH SAID, "RESULTS FROM THE FREE PLAY OF FREE INTELLECTS WORKING ON SUBJECTS OF THEIR OWN CHOICE IN THE MANNER DICTATED BY THEIR CURIOSITY FOR EXPLORATION OF THE UNKNOWN."[3]

A MAJOR REASON FOR OUR EMPHASIS UPON FREEDOM AND FLEXIBILITY IN SCIENTIFIC SUPPORT AND FOR DEFENSE OF AN OPEN SYSTEM BASED UPON THE CREATIVE INITIATIVE OF THE INDIVIDUAL SCIENTIST OR RESEARCH GROUP IS THAT ONE CANNOT PREDICT WHERE A DISCOVERY WILL HAVE ITS MAJOR CLINICAL APPLICATION. THERE ARE NOTABLE EXAMPLES WHERE MAJOR RESEARCH FINDINGS EMERGED FROM AN UNEXPECTED QUARTER FROM SCIENTISTS FOLLOWING LEADS AND GAINING ADVANCES WHICH COULD NEVER HAVE BEEN ANTICIPATED OR PLANNED BEFORE HAND. A RECENT EXAMPLE IS THE STORY OF LYME ARTHRITIS, A DISEASE WHICH CAUSES BOUTS OF ARTHRITIS AND, IN SOME CASES, OTHER SERIOUS ACUTE SYMPTOMS. RHEUMATOLOGISTS AND EPIDEMIOLOGISTS AT YALE, SUPPORTED BY THE NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES, DISCOVERED THE DISEASE AND POSTULATED THAT IT WAS ASSOCIATED WITH CERTAIN TYPES OF SMALL TICKS. BUT IT WAS AN ENTOMOLOGIST WORKING WITH THE NATIONAL INSTITUTE

OF ALLERGY AND INFECTIOUS DISEASES IN OUR ROCKY MOUNTAIN LABORATORY IN HAMILTON, MONTANA, WHO LINKED A NEWLY DISCOVERED TYPE OF BACTERIA, A SPIROCHETE, CARRIED BY THE TICK-VECTOR, TO LYME ARTHRITIS. THIS PROGRESS COULD NOT HAVE BEEN MADE HAD NOT THE CHALLENGE BEEN TAKEN UP BY AN INDIVIDUAL RESEARCHER WITH PARTICULAR EXPERTISE PLUS THE FREEDOM TO PROCEED. THE LYME ARTHRITIS DISCOVERY IS ALSO A TESTIMONIAL TO THE BENEFITS THAT CAN ACCRUE WHEN SCIENTISTS FROM VARIOUS DISCIPLINES (IN THIS CASE, EPIDEMIOLOGY, IMMUNOLOGY, AND ENTOMOLOGY) COLLABORATE FULLY.

A SECOND NOTABLE EXAMPLE IS THE STORY OF THE VIRAL ASSOCIATION IN JUVENILE DIABETES. ALTHOUGH ONE OF OUR INSTITUTES, THE NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES, SUPPORTS MUCH OF THE BASIC RESEARCH RELATED TO DIABETES, THE VIRUS FINDING EMERGED FROM A SMALL GROUP OF INVESTIGATORS WORKING UNDER THE AUSPICES OF THE NATIONAL INSTITUTE OF DENTAL RESEARCH. THE SCIENTISTS, LED BY A VIROLOGIST, PRODUCED THE FIRST DIRECT EVIDENCE THAT VIRUSES ARE CAPABLE OF CAUSING DIABETES IN HUMAN BEINGS. IN 1978, THE NIDR SCIENTISTS LEARNED OF A TEN-YEAR-OLD BOY WHO HAD DIED FOLLOWING AN INFLUENZA-LIKE ILLNESS OF THREE DAYS' DURATION. THE SCIENTISTS WERE IMMEDIATELY INTERESTED IN THE CASE SINCE THE BOY WAS DIABETIC. MOREOVER, THE SIGNS OBSERVED AT AUTOPSY WERE REMINISCENT OF THOSE THEY HAD OBSERVED IN MICE INFECTED WITH DIABETES-CAUSING VIRUSES. USING TECHNIQUES THEY HAD DEVELOPED IN STUDYING MICE, THE SCIENTISTS MANAGED TO ISOLATE A COXSACKIE VIRUS FROM PANCREATIC CELLS. THEN, STRAINS OF MICE DEVELOPED IN THE LABORATORY, SOME SUSCEPTIBLE, SOME RESISTANT TO DIABETES, WERE INOCULATED WITH THE VIRUS FROM THE CHILD'S PANCREAS. WITHIN A WEEK, A HIGH PERCENTAGE OF THE SUSCEPTIBLE MICE HAD DEVELOPED DIABETES, GIVING STRONG EVIDENCE THAT THE CHILD'S DIABETES HAD INDEED BEEN INDUCED BY THE VIRUS.

AS SO OFTEN IS TRUE OF CREATIVE RESEARCH, THESE TWO DISCOVERIES HAVE RAISED AS MANY RESEARCH QUESTIONS AS THEY HAVE ANSWERED. BUT THE EXAMPLES SERVE TO ILLUSTRATE THAT BIOMEDICAL RESEARCH IS STILL AT A POINT WHERE THE CREATIVE IDEAS OF INDIVIDUALS PLAY A LARGE ROLE.

IN AN EFFORT TO ENCOURAGE SUCH "FREE ENTERPRISE" RESEARCH, NIH HAS HISTORICALLY RELIED UPON THE INVESTIGATOR-INITIATED PROJECT GRANT AS ITS PRIMARY MECHANISM FOR THE SUPPORT OF BIOMEDICAL RESEARCH. SUCH GRANTS ARE AN IMPORTANT ELEMENT IN ANOTHER GUIDING PRINCIPLE HELD BY THE NIH--THE NEED TO PROVIDE FOR OPPORTUNITIES FOR NEW INVESTIGATORS TO GAIN ACCESS TO RESEARCH GRANTS; THAT IS, THE ABSOLUTE NECESSITY FOR ASSURING THAT AN ADEQUATE NUMBER OF THE FINEST AND BRIGHTEST YOUNG MINDS IN THE CURRENT AND COMING GENERATIONS FIND CAREERS IN BIOMEDICAL RESEARCH. AN ADEQUATE NUMBER OF FIRST-CLASS BIOMEDICAL RESEARCH SCIENTISTS IN THE 1980s AND 1990s CAN ONLY BE MAINTAINED IF GRADUATE SCHOOLS AND

ACADEMIC HEALTH CENTERS ARE SUCCESSFUL IN NURTURING THE RESEARCH CAREER INTERESTS OF THE YOUNG PEOPLE WHO COME TO THEM FOR TRAINING, AND IF THERE ARE ATTRACTIVE EMPLOYMENT OPPORTUNITIES AHEAD THIS YEAR, GRADUATING PH.D. SCIENTISTS ARE SHOWING AN INTEREST IN POSTDOCTORAL FELLOWSHIPS IN ACADEMIC INSTITUTIONS AND AN INTEREST IN GOING DIRECTLY INTO INDUSTRY.

NIH HAS A ROLE TO PLAY HERE AS WELL, SINCE IT IS IMPORTANT THAT SUCH YOUNG PEOPLE HAVE A REASONABLE EXPECTATION THAT THEY WILL HAVE OPPORTUNITIES TO APPLY THEMSELVES TO RESEARCH STUDIES IN THEIR FIELDS OF INTEREST WHEN THEIR TRAINING IS COMPLETED. IT IS OBVIOUS THAT AMPLE FUNDS FOR THE SUPPORT OF PROJECT RESEARCH ARE AN INCENTIVE FOR YOUNG SCIENTISTS TO CHOOSE RESEARCH AS A CAREER AND TO STAY WITH IT.

ANOTHER EFFECT OF THE FEDERAL INVESTMENT IN BIOMEDICAL RESEARCH THROUGH THE NATIONAL INSTITUTES OF HEALTH IS WORTHY OF NOTE. EARLIER THIS YEAR, SCIENCE MAGAZINE PUBLISHED A SPECIAL ISSUE DEVOTED TO NEW BIOTECHNOLOGY. THE FIRST ARTICLE WAS AN OVERVIEW BY EDITOR PHILIP H. ABELSON OF THE 21 ARTICLES THAT FOLLOWED ON GENE SPLICING, MONOCLONAL ANTIBODIES, PROTEIN ENGINEERING, AGRICULTURAL RESEARCH, AND MICROBIOLOGICAL ENGINEERING. ABELSON GAVE MUCH CREDIT TO NIH. HE WROTE: "THIS POTENTIALLY RICH HARVEST IS THE RESULT OF WISE INVESTMENTS IN BASIC BIOLOGICAL RESEARCH BY THE NATIONAL INSTITUTES OF HEALTH." HE ALSO NOTED THAT "OTHER CONSEQUENCES OF NIH SUPPORT HAVE NOT BEEN EMPHASIZED . . . NIH FUNDS COMBINED WITH THE ATTRACTION OF RESEARCH OPPORTUNITIES IN BIOMEDICINE HAVE LURED MANY OF THE MOST INTELLIGENT AND CREATIVE SCIENTISTS INTO FUNDAMENTAL BIOLOGY. MANY OF THESE PEOPLE ARE NOW KEY MEMBERS OF THE NEW DYNAMIC BIOENGINEERING COMPANIES. NIH FUNDS ALSO HAVE CREATED A MARKET FOR INSTRUMENTATION AND SPECIAL PRODUCTS USED IN RESEARCH. THE INSTRUMENTATION AVAILABLE IN THIS COUNTRY IS SUPERB AND IS CONSTANTLY BEING IMPROVED. COMPANIES PROVIDING ITEMS USED IN RESEARCH, SUCH AS ENZYMES, FOLLOW TRENDS CLOSELY AND ARE QUICK TO SUPPLY NEEDED MATERIALS, CULTURES, OR ANIMALS."[4]

BUT INDUSTRY'S INVOLVEMENT IN THE PROCESS OF FEDERAL-ACADEMIC BIOMEDICAL RESEARCH EXTENDS FAR BEYOND ITS ROLE AS SUPPLIER OF MATERIALS AND INSTRUMENTS. IN A NUMBER OF NOTABLE INSTANCES INDUSTRY HAS JOINED IN FULL PARTNERSHIP WITH ACADEMIC RESEARCH CENTERS. AT THE SAME TIME, BIOMEDICAL RESEARCH ITSELF HAS ENTERED THE MARKET PLACE AND MOLECULAR BIOLOGY, FOR EXAMPLE, HAS BECOME BIG BUSINESS. DURING THE PAST FEW YEARS, THERE HAS BEEN A SPECTACULAR MOVEMENT AMOUNTING ALMOST TO AN EXPLOSION IN BIOTECHNOLOGY. RESEARCHERS AND INDUSTRIALISTS HAVE MOVED QUICKLY AND WITH DETERMINATION TO EXPLOIT MOLECULAR BIOLOGY FOR USEFUL AND PROFITABLE PRODUCTS. THE ROOTS OF MANY OF THESE PRODUCTS LIE IN RECOMBINANT DNA AND MONOCLONAL ANTIBODY TECHNOLOGIES CONCEIVED AND INITIALLY

DEVELOPED ALMOST ENTIRELY IN UNIVERSITY SETTINGS OR IN FEDERAL LABORATORIES. OFTEN THE UNIVERSITY RESEARCH WAS CARRIED OUT WITH FEDERAL FUNDING.

IF THE HISTORY OF THE PAST FEW YEARS GIVES ANY INDICATION OF THE FUTURE, WE CAN EXPECT THE RAPID DEVELOPMENT OF MANY THERAPEUTIC AGENTS AND OTHER PRODUCTS WHICH CAN BE OF INCALCULABLE BENEFIT TO THE PUBLIC.

IN SOME QUARTERS, THERE ARE CONCERNS THAT THE MOMENTUM AND MAGNITUDE OF THESE NEW ACTIVITIES COULD RESULT IN FUNDAMENTAL CHANGES IN THE WAY RESEARCH IS CONDUCTED, AND THAT THE NEW TIES BETWEEN GOVERNMENT, THE UNIVERSITIES, AND INDUSTRY WILL SO DISTORT THE OBJECTIVES AND PROCESS OF SCIENCE THAT ULTIMATELY THE PUBLIC WILL BE THE LOSER.

LAST DECEMBER, I WAS ASKED TO SPEAK AT A NATIONAL CONFERENCE ON UNIVERSITY-CORPORATE RELATIONS IN SCIENCE AND TECHNOLOGY AND IN THAT CONTEXT TO ADDRESS FEDERAL CONCERNS. AS I THOUGHT ABOUT THE GOVERNMENT-INDUSTRY-ACADEMIC TRIANGLE IN THE RESEARCH ENTERPRISE, I WAS REMINDED THAT SOME OF THE CONCERNS ABOUT THIS RELATIONSHIP RESEMBLED THOSE THAT HAVE BEEN EXPRESSED ABOUT THE BERMUDA TRIANGLE, THAT MYTHICAL AREA WHERE IT IS SAID THERE IS A MYSTERIOUS FORCE FIELD THAT SWALLOWS UP THOSE WHO ENTER.

SOME OF THE ISSUES RAISED BY THE NEW UNIVERSITY-CORPORATE ARRANGEMENTS FOR THE PURSUIT OF RESEARCH ARE AS MYTHICAL AS THE BERMUDA TRIANGLE, WHILE OTHERS ARE REAL, AND STILL OTHERS ARE OF AMBIGUOUS POTENTIAL. THE ISSUES AND THE PROBLEMS ARE PRIMARILY AT THE INTERFACE BETWEEN ACADEMIA AND THE CORPORATE WORLD. THERE HAVE BEEN SUGGESTIONS THAT THE NIH TAKE SOME KIND OF AN ACTIVE ROLE IN DEVELOPING THESE NEW RELATIONSHIPS. WE HAVE NOT DONE SO. WE BELIEVE IT PREFERABLE THAT THE NEW FORMS OF JOINT ENDEAVOR EVOLVE AS THEY HAVE WITH GOVERNMENT PLAYING A FACILITATIVE ROLE. IT IS OUR POSITION THAT GOVERNMENT SUPPORTS RESEARCH BECAUSE IT IS IN THE NATIONAL INTEREST AND ESSENTIAL TO THE WELFARE AND SECURITY OF THE NATION. IT SUPPORTS BOTH THE ACQUISITION OF NEW KNOWLEDGE AND THE APPLICATION OF SUCH KNOWLEDGE TO THE SOLUTION OF SOCIETAL PROBLEMS. MAINTAINING A HEALTHY ECONOMY IS ALSO AN IMPORTANT GOVERNMENT RESPONSIBILITY. TECHNOLOGY TRANSFER IS AN ENERGETIC EMPHASIS OF GOVERNMENT TO INSURE THAT THE PUBLIC GOOD IS SERVED BOTH THROUGH THE APPROPRIATE APPLICATION OF RESEARCH RESULTS AND THE DEVELOPMENT OF THE ECONOMIC WELL-BEING OF THE COUNTRY.

MORE THAN A YEAR AGO, THE HEADS OF 5 MAJOR RESEARCH UNIVERSITIES AND 11 CORPORATIONS MET TOGETHER IN A SMALL PRIVATE CONFERENCE FOR A SEARCHING DISCUSSION OF THE IMPLICATIONS OF ACADEMIA'S COLLABORATION WITH INDUSTRY,

PARTICULARLY IN BIOTECHNOLOGY. IN A REPORT ON THE OUTCOME OF THE CONFERENCE, BARBARA CULLITON, WRITING IN SCIENCE, COMMENTED, "ITS OVERRIDING MESSAGE IS THAT THERE IS AS YET NO CERTAINTY ABOUT HOW FAR TO GO IN WRITING RULES AND NO PRESUMPTION THAT THEY NEED TO BE THE SAME FOR EVERY CAMPUS." THEN, MS. CULLITON, IN HER OWN UNDERSTATED STYLE, NOTED "PLURALISM AND A CERTAIN MEASURE OF CONFUSION PREVAIL."[5]

THE CONFEREES DID CONCUR, HOWEVER, THAT THE UNIVERSITIES' INTEREST IN INDUSTRY IS NOT ENTIRELY SELF-SEEKING. THEY VIEWED SUCH COLLABORATION AS PROMOTING THE PUBLIC GOOD AND SO JUSTIFIED THE FACT THAT CORPORATE PROFIT WILL BE MADE FROM RESEARCH THAT WAS PUBLICLY FUNDED IN THE FIRST PLACE. THE CONFERENCE'S CONCLUDING STATEMENT ASSERTED THAT "THERE ARE SEVERAL STRONG MOTIVATIONS FOR ACADEMIC INSTITUTIONS AND THEIR FACULTIES TO SEEK INDUSTRY SUPPORT FOR RESEARCH. FIRST, THERE IS A GENUINE INTEREST IN FACILITATING THE TRANSFER OF TECHNOLOGY FROM DISCOVERY TO USE TO CONTRIBUTE TO THE HEALTH AND PRODUCTIVITY OF SOCIETY."[6] THE SAME SANGUINE VIEW OF THE RELATIONSHIP WAS EXPRESSED BY PRESIDENT DEREK BOK IN HIS ANNUAL REPORT TO THE HARVARD OVERSEERS WHEN HE SAID, "WITH HARD WORK AND A BIT OF LUCK, A UNIVERSITY MIGHT CONCEIVABLY CONTRIBUTE TO THE NATION'S PROSPERITY IN WAYS THAT COULD INCREASE ITS OWN RESOURCES IN ORDER TO STRENGTHEN ITS RESEARCH EFFORT TO MAKE STILL FURTHER CONTRIBUTIONS TO THE ECONOMY, AND SO ON, IN AN ENDLESS SYNERGISTIC PROCESS."[7]

LAST YEAR, THE AMERICAN FEDERATION FOR CLINICAL RESEARCH SPONSORED A SYMPOSIUM ON "CHANGING PATTERNS OF BIOMEDICAL RESEARCH FUNDING." THE SPOKESMAN PRESENTING INDUSTRY'S VIEW WAS MY FRIEND, DR. THEODORE COOPER, FORMERLY HEAD OF ONE OF NIH'S LARGER INSTITUTES, LATER ASSISTANT SECRETARY FOR HEALTH, AND NOW A LEADER IN THE PHARMACEUTICAL INDUSTRY AS EXECUTIVE VICE PRESIDENT OF THE UPJOHN COMPANY. COMMENTING ON THE RELATIVE DECLINE IN FEDERAL SUPPORT OF BIOMEDICAL RESEARCH IN ACADEMIC INSTITUTIONS, DR. COOPER NOTED THAT "INDUSTRY SHOULD AND WILL SUPPORT MORE RESEARCH IN ACADEMIA, BUT NOT BECAUSE THERE IS A SHORTFALL IN FEDERAL PROGRAMS. THEY WILL EXPAND THEIR EFFORTS IN THE INTEREST OF THEIR STOCKHOLDERS BECAUSE IT WILL HELP THEM SUCCEED. THERE MAY BE A DOUBLING IN CERTAIN SECTORS OF THE CORPORATE RESEARCH EFFORT OVER THE NEXT FIVE YEARS. BUT THAT WILL NOT MAKE UP FOR THE EROSION OF FEDERAL SUPPORT. INDUSTRY WILL JOIN IN SUPPORT OF THE INTELLECTUAL OVERHEAD OF THE ACADEMIC ESTABLISHMENT. THERE WILL BE NEW KINDS OF RELATIONSHIPS EVOLVING. SOME WILL SUCCEED, BUT NOT ALL IDEAS WILL SURVIVE."

DR. COOPER WENT ON TO SAY, "IT MAY APPEAR UNNATURAL FOR INDUSTRY TO ADVOCATE EXPANSION OF FEDERAL PROGRAMS. IT SEEMS CONTRARY TO WHAT IS GIVEN AS THE CONSERVATIVE CONVERSION. PERISH THE THOUGHT! THE PHILOSOPHICAL DEBATE IS NOT OVER HAVING ANY GOVERNMENT PROGRAMS; RATHER IT IS OVER WHICH ONES. SUPPORTING RESEARCH IS SEEN BY MOST CONSERVATIVES AS A PROPER ROLE FOR GOVERNMENT,

PARTICULARLY IN THE HEALTH FIELD." DR. COOPER THEN LISTED FIVE REASONS WHY INDUSTRY IS INTERESTED IN REGAINING STRONG ARRANGEMENTS WITH ACADEMIA. HE CALLED THEM HIS FIVE P's: (1) TO GAIN PATENTABLE IDEAS OR ENTITIES; (2) TO HAVE ACCESS TO PATIENTS FOR CLINICAL TRIALS; (3) TO HAVE PUBLICATIONS OF CLINICAL STUDIES WHICH ARE VALUABLE FOR PROMOTION AIDS; (4) TO ATTRACT PERSONNEL TO THE COMPANY AS STAFF OR CONSULTANTS, AND (5) TO HAVE THE PRESTIGE OF ASSOCIATION WITH ITS IMPLIED RELIABILITY AND QUALITY. THEN HE SAID, "THESE FIVE P's, WHEN EFFECTIVELY ORCHESTRATED, WILL YIELD A SIXTH BIG P-- PROFIT, AND PROFIT IS WHAT INSURES FUTURE INVESTMENTS."[8]

IN DISCUSSING THE EVOLUTION OF FORMAL RESEARCH PARTNERSHIPS INVOLVING ACADEMIC INSTITUTIONS, INDUSTRY, AND THE GOVERNMENT, IT IS WELL TO KEEP IN MIND THAT THE NATURE OF THE SCIENTIFIC ENTERPRISE IS SUCH THAT INFORMAL NETWORKS OF COLLABORATION AMONG SCIENTISTS HAVE ALWAYS EXISTED AND WITH LITTLE REGARD FOR THEIR INDIVIDUAL ORGANIZATIONAL AFFILIATIONS. THE NATURE OF THIS COLLABORATION IS REVEALED IN THE FOOTNOTES OR TEXTS OF ALMOST ANY REVIEW ARTICLE ON A SCIENTIFIC SUBJECT.

TO ILLUSTRATE MY POINT, PERMIT ME TO CITE, AS A RANDOM EXAMPLE, AN ARTICLE THAT APPEARED IN THE AUGUST EDITION OF SCIENTIFIC AMERICAN.[9] THE PAPER WAS WRITTEN BY DR. SIDNEY PESTKA, HEAD OF THE LABORATORY OF MOLECULAR GENETICS AT THE ROCHE INSTITUTE OF MOLECULAR BIOLOGY. THE SUBJECT WAS "THE PURIFICATION AND MANUFACTURE OF HUMAN INTERFERONS." IN THE ARTICLE, DR. PESTKA REVIEWED THE HISTORY OF INTERFERON--AN AGENT RELEASED BY CELLS EXPOSED TO A VIRUS THAT ENABLES OTHER CELLS TO RESIST VIRAL INFECTION. SOME 40 SCIENTISTS ARE MENTIONED IN THE TEXT OF THE ARTICLE FOR THEIR SIGNIFICANT CONTRIBUTIONS RELATED TO INTERFERON SINCE ITS DISCOVERY IN 1957. THE SCIENTISTS DID THE WORK FOR WHICH THEY WERE CITED AT 25 DIFFERENT INSTITUTIONS, INCLUDING SIX MAJOR AMERICAN ACADEMIC INSTITUTIONS, ACADEMIC INSTITUTIONS IN CANADA, SWEDEN, SWITZERLAND, FRANCE, AND BELGIUM, TWO INSTITUTES OF THE NATIONAL INSTITUTES OF HEALTH, FIVE MAJOR INDUSTRIAL OR PHARMACEUTICAL COMPANIES, AND RESEARCH INSTITUTES IN JAPAN, FINLAND, GREAT BRITAIN, AND THE UNITED STATES. PERHAPS EVEN MORE SIGNIFICANT IS THE FACT THAT, IN MANY INSTANCES, PAIRS OR GROUPS OF SCIENTISTS COLLABORATED ACROSS INDUSTRIAL/ACADEMIC, GOVERNMENT/ACADEMIC, AND GOVERNMENT/INDUSTRIAL ORGANIZATIONAL LINES, AS WELL AS ACROSS INTERNATIONAL BOUNDARIES.

ANOTHER NOTABLE EXAMPLE OF SUCCESS THROUGH SUCH WIDESPREAD COLLABORATION IS THE VACCINE TO COMBAT HEPATITIS B VIRUS, WHICH IS THE CAUSE OF A DEBILITATING LIVER DISEASE. THE VACCINE, LICENSED LESS THAN TWO YEARS AGO, WAS MADE POSSIBLE BY NIH-SPONSORED BASIC RESEARCH AND YEARS OF PAINSTAKING RESEARCH AND DEVELOPMENT EFFORTS BY SCIENTISTS IN GOVERNMENT, ACADEMIA AND INDUSTRY. THIS SAGA

ILLUSTRATES THE IMPORTANCE OF SERENDIPITY AND IS ILLUSTRATIVE OF THE ROLES IN RESEARCH TO BE PLAYED BY GOVERNMENT, INDUSTRY AND THE UNIVERSITY.

THE DISCOVERY THAT REVOLUTIONIZED THE STUDY OF HEPATITIS CAME FROM AN ENTIRELY UNEXPECTED QUARTER. BARUCH S. BLUMBERG, AN IMMUNOLOGIST WITH AN INTEREST IN HUMAN GENETICS, IN 1963 BECAME INTRIGUED WHEN A PECULIAR SUBSTANCE IN THE BLOOD FROM AN AUSTRALIAN ABORIGINE CAUGHT HIS ATTENTION. INITIALLY, HE THOUGHT HE HAD DISCOVERED AN EVOLUTIONARY MARKER IN THE BLOOD OF A PRIMATIVE PEOPLE. THEN HE RECOGNIZED THAT THE SUBSTANCE MIGHT BE A PROTEIN FRAGMENT LEFT BY AN EARLIER INFECTION. HE DOGGEDLY FOLLOWED UP ON THE LEAD AND WITHIN THREE YEARS IT BROUGHT HIM TO THE DISCOVERY OF THE HEPATITIS B VIRUS. THE WORK, WHICH STARTED AS A BASIC INQUIRY, HAS LED TO MANY DIFFERENT LINES OF RESEARCH TO A NUMBER OF MAJOR CLINICAL ADVANCES AND THE ULTIMATE DEVELOPMENT OF THE VACCINE. ALONG THE WAY BLUMBERG WON A NOBEL PRIZE. IN HIS NOBEL ADDRESS HE SAID, "AT THE OUTSET WE HAD NO SET VIEWS ON WHERE THIS PATH MIGHT LEAD. I COULD NOT HAVE PLANNED THE INVESTIGATION AT ITS BEGINNING TO FIND THE CAUSE OF HEPATITIS B." BUT BETWEEN BLUMBERG'S EARLY DISCOVERY AND THE DEVELOPMENT OF THE VACCINE LAY A WHOLE RANGE OF RESEARCH STUDIES, BASIC AND CLINICAL. PRODUCTION OF A SAFE AND EFFECTIVE VACCINE TURNED OUT TO BE A HIGHLY COMPLICATED, TECHNOLOGICAL PROBLEM FOR THE PHARMACEUTICAL COMPANY THAT ACCEPTED THE CHALLENGE. THIS WAS FOLLOWED BY EXPENSIVE CLINICAL TRIALS IN 1978 WITH SEVERAL GROUPS OF VOLUNTEERS WHO WERE AT PARTICULARLY HIGH RISK. THESE STUDIES WERE CONDUCTED IN DOUBLE-BLIND FASHION SO THAT NEITHER THE SCIENTISTS NOR THE VOLUNTEERS KNEW WHO RECEIVED THE VACCINE AND WHO RECEIVED THE PLACEBO. BY 1980 THE RESULTS INDICATED THAT THE TRIAL HAD BEEN HIGHLY SUCCESSFUL.

ONCE AGAIN, ACTIVE COOPERATION AMONG SCIENTISTS IN GOVERNMENT, INDUSTRY AND ACADEMIA PRODUCED RESULTS OF SIGNIFICANCE TO THE WELL-BEING OF CURRENT AND FUTURE GENERATIONS AND TO THE HEALTH OF THE ECONOMY. THE CENTERS FOR DISEASE CONTROL ESTIMATE THE COST OF HOSPITAL TREATMENT ALONE FOR HEPATITIS B, THE MINIMUM THAT CAN BE SAVED BY USING THE VACCINE, AT ABOUT $4.3 MILLION PER WEEK--A PRIME EXAMPLE OF HEALTH AND ECONOMIC BENEFIT FROM RESEARCH AND DEVELOPMENT COLLABORATION.

THE HEPATITIS B STORY IS BUT ONE MORE EXAMPLE CONFIRMING THE TRUTH THAT BEFORE THERE CAN BE INTELLIGENTLY CONDUCTED APPLIED RESEARCH, BEFORE THERE CAN BE DEMONSTRATIONS OR CLINICAL TRIALS, OR BEFORE THERE COULD BE PUBLIC DISSEMINATION OF TECHNIQUES, THERE MUST BE ENOUGH PRODUCTIVE BASIC RESEARCH TO PROVIDE THE FUNDAMENTAL SCIENCE FROM WHICH THESE EFFORTS FLOW.

NOTWITHSTANDING THE FACT THAT THE AREAS OF COLLABORATION BETWEEN THE UNIVERSITIES AND INDUSTRY HAVE BROADENED SIGNIFICANTLY AND PROMISE TO CONTINUE

THAT EXPANSION, THE GOVERNMENT WILL CONTINUE AS THE PRINCIPAL SOURCE OF FUNDING FOR BASIC RESEARCH.

DR. GEORGE KEYWORTH, THE PRESIDENT'S SCIENCE ADVISOR, PUT IT THIS WAY, "BASIC RESEARCH WARRANTS GOVERNMENT SUPPORT BECAUSE IT IS AN INVESTMENT IN THE FUTURE--IN A BETTER QUALITY OF LIFE, BETTER SECURITY, A BETTER ECONOMY, AND SIMPLY BETTER UNDERSTANDING."[10] HE WENT ON TO EMPHASIZE THAT BASIC RESEARCH IS A RESPONSIBILITY OF GOVERNMENT FOR THE DUAL REASONS THAT IT BENEFITS THE PEOPLE AND THE ECONOMY AND THAT THERE IS NO OTHER SOURCE OF SUPPORT FOR BASIC RESEARCH ON THE SCALE REQUIRED. ON THE BASIS OF THIS RESPONSIBILITY OF THE FEDERAL GOVERNMENT, WE MUST BE CONCERNED THAT THERE IS A CRITICAL NEED TO REVITALIZE THE INSTRUMENTATION AND FACILITY BASE ON WHICH FUTURE SCIENTIFIC AND TECHNOLOGICAL ADVANCES DEPEND. INVESTIGATORS NEED FIRST-RATE EQUIPMENT AND A CONTEMPORARY ENVIRONMENT IN WHICH TO DO RESEARCH. PROGRESS IN MEDICAL RESEARCH DEPENDS HEAVILY UPON STATE OF THE ART INSTRUMENTS; MANY ADVANCES IN BASIC AND CLINICAL RESEARCH CAN ONLY BE MADE THROUGH MODERN ADVANCED INSTRUMENTATION. UNDERINVESTMENT IN INSTRUMENTATION IN THE PAST DECADE HAS LED TO CONCERN REGARDING STATE OF THE ART INSTRUMENTATION.

ACCORDING TO A STUDY CONDUCTED FOR THE NATIONAL SCIENCE FOUNDATION BY THE ASSOCIATION OF AMERICAN UNIVERSITIES IN 1981, 50 PERCENT OF THE INSTRUMENTATION INVENTORY WAS PURCHASED PRIOR TO 1974. THUS, MORE THAN HALF OF UNIVERSITY INSTRUMENTATION IS AT LEAST NINE-TO-TEN-YEARS OLD. THE SAME STUDY REVEALED A STRIKING DISPARITY IN THE AGE OF UNIVERSITY AND INDUSTRY INSTRUMENTATION. THE MEDIAN AGE OF THE UNIVERSITY INSTRUMENTATION IS TWICE THAT OF INSTRUMENTATION IN INDUSTRIAL LABORATORIES. INDUSTRIAL LABORATORIES APPARENTLY CAN MOBILIZE RESOURCES RAPIDLY TO MEET SUDDENLY ARISING OPPORTUNITIES, WHEREAS UNIVERSITY INSTRUMENTATION IS ACQUIRED IN BITS AND PIECES OVER A NUMBER OF YEARS, AND DEPENDS HEAVILY UPON OUTSIDE SOURCES OF MONEY.

ESTIMATES OF THE BIOMEDICAL INSTRUMENTION DEFICIT INDICATE THAT FOR LARGE AND COMPLEX INSTRUMENTS ALONE, AN AMOUNT OF $20 MILLION A YEAR FOR FIVE YEARS WOULD BE NEEDED TO MAINTAIN THE ADEQUACY OF THE NATION'S BIOMEDICAL RESEARCH CAPACITY. WE DO NOT KNOW AT THIS TIME THE MAGNITUDE OF THE TOTAL INSTRUMENT GAP. EQUIPMENT SHORTAGES AND OBSOLESCENCE OF SCIENTIFIC INSTRUMENTATION ARE A GROWING PROBLEM; A BACKLOG OF NEED HAS ACCUMULATED; RESEARCH EQUIPMENT IS OLD AND DETERIORATING; AND THERE IS A SHORT SUPPLY OF STATE OF THE ART EQUIPMENT.

IN AN EFFORT TO DEAL WITH AT LEAST ONE OF THE MAJOR ELEMENTS OF THIS PROBLEM, THE NATIONAL INSTITUTES OF HEALTH MORE THAN TWO YEARS AGO INITIATED THE SHARED INSTRUMENTATION GRANT PROGRAM. OUR EXPERIENCE OVER THIS TWO-YEAR PERIOD SHOWS THAT THE PROGRAM IS BEGINNING TO ADDRESS THE INSTRUMENT NEEDS OF THE BASIC AND CLINICAL SCIENTISTS. IN FY 1982 THE PROGRAM RECEIVED 206 APPLICATIONS

REQUESTING $39 MILLION. AWARDS TOTALING $3.7 MILLION WERE MADE TO 23 INSTITUTIONS FOR A VARIETY OF INSTRUMENTS, INCLUDING ELECTRON MICROSCOPES, COMPUTER GRAPHICS SYSTEMS, HIGH-SENSITIVITY NUCLEAR MAGNETIC RESONANCE SYSTEMS AND MASS SPECTROMETORS, AND CELL SORTERS. IN FY 83 THE PROGRAM RECEIVED 160 APPLICATIONS REQUESTING $30 MILLION. WE EXPECT TO HAVE AWARDED ABOUT $14 MILLION DURING FY 83. SHARED INSTRUMENTATION REDUCES THE COST OF ADVANCED TECHNOLOGY REQUIRED FOR BIOMEDICAL RESEARCH AT THE CUTTING EDGE OF SCIENCE. LOCAL CONTROL AND INSTITUTIONAL PLANNING FOR RESEARCH EQUIPMENT NEEDS OPTIMIZE THE EQUIPMENT INVESTMENT RETURNS THROUGH SHARING AMONG DEPARTMENTS WITHIN AN INSTITUTION AND AMONG INSTITUTIONS IN A PARTICULAR REGION. AN INCREASED RELIANCE ON SHARED INSTRUMENTS EFFECTS POSITIVE INTERACTION AMONG INVESTIGATORS AND GRADUATE STUDENTS, PARTICULARLY ACROSS DEPARTMENTAL AND DISCIPLINARY LINES.

THERE IS AMPLE INFORMATION TO SUGGEST THAT THE NEED FOR CONSTRUCTION, REPAIR OR RENOVATION OF HEALTH RESEARCH FACILITIES IS PROBABLY SUBSTANTIAL, ALTHOUGH EXISTING DATA ARE FAR FROM COMPREHENSIVE OR DEFINITIVE. NIH INVOLVEMENT IN CONSTRUCTION FOR NON-FEDERAL HEALTH RELATED RESEARCH FACILITIES DATES BACK TO 1948 WHEN APPROPRIATIONS WERE MADE AVAILABLE TO THE NATIONAL CANCER INSTITUTE FOR RESEARCH CONSTRUCTION. DURING THE 35-YEAR PERIOD SINCE THEN, THE NIH HAS SPENT APPROXIMATELY $840 MILLION FOR SUCH PURPOSES. HOWEVER, FEDERAL SUPPORT FOR RESEARCH AND DEVELOPMENT PLANT FACILITIES HAS DECREASED DRAMATICALLY SINCE 1965. MANY OF THE FACILITIES BENEFITING FROM THE MAJOR NIH CONSTRUCTION PROGRAM, THE HEALTH RESEARCH FACILITIES PROGRAM, ARE MORE THAN 20 YEARS OLD, OR ARE RAPIDLY APPROACHING THAT MARK.

MEANWHILE, DRAMATIC CHANGES HAVE OCCURRED IN RESEARCH LABORATORY REQUIREMENTS BROUGHT ABOUT BY THE EXPLOSION IN THE KNOWLEDGE BASE, THE DEVELOPMENT OF NEW TECHNOLOGIES, AND MORE EFFECTIVE HANDLING AND PROCESSING OF INFORMATION. THE STORAGE AND DISPOSAL OF TOXIC WASTE MATERIALS IS ALSO A SERIOUS PROBLEM FOR THE MODERN LABORATORY. RESEARCH SPACE OF 20 YEARS AGO, FOR THE MOST PART, CANNOT ACCOMMODATE RESEARCH REQUIREMENTS OF TODAY WITHOUT RENOVATION.

THE LAST EXAMINATION OF THE NEED FOR HEALTH RESEARCH FACILITIES WAS A SURVEY CONDUCTED BY THE AMERICAN COUNCIL ON EDUCATION IN 1976. THE REPORT OF THIS STUDY, BASED ON INFORMATION PROVIDED BY 155 PH.D.-GRANTING INSTITUTIONS, ADDRESSED THE STATUS OF ACADEMIC HEALTH RESEARCH FACILITIES' NEW CONSTRUCTION IN PROGRESS AND PLANS FOR RESEARCH AND DEVELOPMENT PLANT EXPANSION FOR THE FOLLOWING FIVE YEARS. THE PRINCIPAL FINDINGS OF THE STUDY INCLUDED THE FACT THAT 23 MILLION NET SQUARE FEET OF SPACE WERE DEVOTED TO HEALTH RESEARCH AT THOSE INSTITUTIONS INCLUDED IN THE SURVEY, AND THAT OF THIS AMOUNT 29 PERCENT OF THE SPACE REQUIRED RENOVATION OR REPLACEMENT. THE COST FOR NEW CONSTRUCTION AND

RENOVATION DURING 1975 WAS ESTIMATED AT $547 MILLION AND OVER $560 MILLION FOR THE FOLLOWING FIVE YEARS. PUBLIC FINANCING WAS VIEWED BY THE INSTITUTIONS AS A SIGNIFICANT SOURCE OF THE REQUIRED FUNDING. A SUBSTANTIAL COMPONENT OF THIS AMOUNT REPRESENTS UNFILLED NEEDS IN AND FUTURE REQUIREMENTS FOR FACILITIES FOR THE CARE OF RESEARCH ANIMALS.

OBVIOUSLY, THE CURRENT AND FUTURE REQUIREMENTS FOR INSTRUMENTATION AND FACILITIES ARE MATTERS ABOUT WHICH ALL OF THE PARTNERS IN BIOMEDICAL RESEARCH MUST BE CONCERNED.

IN CONCLUSION, I WILL TURN FROM ORGANIZATIONS AND BUDGETS TO THE KINDS OF THINGS RESEARCH IS ALL ABOUT--A FEW AREAS OF SCIENTIFIC PROMISE.

FOR EXAMPLE, THE DEVELOPMENT OF RECOMBINANT DNA TECHNOLOGY, AN EXCITING TOOL THAT PERMITS US TO TRANSFER HEREDITARY UNITS FROM ONE SPECIES TO ANOTHER. IT MAKES IT POSSIBLE TO USE BACTERIA AS "FACTORIES" FOR THE PRODUCTION OF VALUABLE SUBSTANCES OF BIOLOGICAL, AGRICULTURAL, AND MEDICAL IMPORTANCE. THIS TECHNIQUE HAS ALREADY LED TO THE SYNTHETIC PRODUCTION OF HUMAN INSULIN, INTERFERON, AND GROWTH HORMONE.

THESE SUBSTANCES HERETOFORE HAVE BEEN AVAILABLE ONLY BY EXTRACTION FROM ANIMAL AND HUMAN TISSUES AND SOME, LIKE GROWTH HORMONE AND INTERFERON, HAVE BEEN EXTREMELY EXPENSIVE. RECOMBINANT DNA-PRODUCED FORMS OF THESE SUBSTANCES ARE NOW BEING TESTED IN NIH-SPONSORED CLINICAL TRIALS TO DETERMINE THEIR EFFECTIVENESS IN TREATING INSULIN-DEPENDENT DIABETES, CERTAIN TYPES OF DWARFISM, AND IN THE CASE OF INTERFERON, ITS EFFECTIVENESS IN TREATING TYPES OF CANCER AND OTHER DISEASE PROBLEMS. RECOMBINANT DNA TECHNOLOGY CAN ALSO BE USED TO PRODUCE LARGE QUANTITIES OF PURE ANTIGEN, WHICH IN TURN CAN BE USED FOR IMMUNIZATION. THIS APPROACH FORMS A CORNERSTONE OF OUR ACCELERATED VACCINE DEVELOPMENT PROGRAM.

ANOTHER AREA OF PROMISE IS IN THE USE OF CELL FUSION TO CREATE HYBRIDOMAS FOR THE PRODUCTION OF HIGHLY SPECIFIC ANTIBODIES TO BE USED FOR SPECIFIC VACCINES, EXTREMELY SENSITIVE DIAGNOSTIC TESTS, AND FOR THE TREATMENT OF MANY DISEASES. THIS TECHNOLOGY MAY PERMIT THE DETECTION OF CANCER AT A VERY EARLY STAGE AND EVENTUALLY THE ANTIBODIES MAY BE USED TO CARRY RADIOACTIVE OR CHEMOTHERAPEUTIC AGENTS TO KILL CANCER CELLS WITHOUT HARMING HEALTHY TISSUE.

I NOTE FROM YOUR PROGRAM THAT PRESENTATIONS ON THESE EXCITING SUBJECTS ARE SCHEDULED FOR THIS AFTERNOON.

REMARKABLE PROGRESS IS BEING MADE IN UNDERSTANDING THE IMMUNE SYSTEM. SCIENTISTS HAVE DISCOVERED GENETIC MECHANISMS THAT CONTROL THE IMMUNE RESPONSE TO SUCH INVADERS AS CANCER CELLS, TRANSPLANTED ORGANS, AND ENVIRONMENTAL

SUBSTANCES THAT CAUSE ALLERGIES. THE KNOWLEDGE TO BE GAINED MAY LEAD TO BETTER STRATEGIES TO SUPPLEMENT NATURAL RESISTANCE IN WARDING OFF JUVENILE ONSET DIABETES, CERTAIN KINDS OF ARTHRITIS, ALZHEIMER'S DISEASE, CHRONIC HEPATITIS, AND TO THE DEVELOPMENT OF BETTER TECHNIQUES FOR ORGAN AND TISSUE TRANSPLANTATION. THE INTENSIVE RESEARCH EFFORT FOCUSED ON ACQUIRED IMMUNE DEFICIENCY SYNDROME, UNDERWAY AT CENTERS IN MANY PARTS OF THE NATION, WILL NOT ONLY HELP US DIAGNOSE, PREVENT AND TREAT THE DISEASE BUT ALSO IT WILL YIELD A DEEPER UNDERSTANDING OF THE HUMAN IMMUNE SYSTEM AND THE PROCESS OF HUMAN CANCER.

ANOTHER ESPECIALLY EXCITING AND EXPANDING AREA IS RESEARCH ON NEUROBIOLOGY. INVESTIGATORS ARE FINDING MORE AND MORE SUBSTANCES THAT HAVE PROFOUND EFFECTS ON THE NERVOUS SYSTEM. ONE FRUITFUL AREA IS THE STUDY OF THE BODY'S NATURAL PAIN KILLERS, THE ENDORPHINS AND OTHER OPIATE-LIKE SUBSTANCES, FROM WHICH WE HOPE TO GAIN A FULLER UNDERSTANDING OF THE MECHANISMS OF BRAIN FUNCTION, DRUG ADDICTION, AND THE TREATMENT OF PAIN.

NEW INSTRUMENTS HAVE BEEN DEVELOPED; E.G., THE PET SCANNER (POSITRON EMISSION TRANSAXIAL TOMOGRAPHY) AND THE NMR SCANNER (NUCLEAR MAGNETIC RESONANCE)--WHICH PROVIDE NON-INVASIVE METHODS FOR THE STUDY OF ORGAN STRUCTURE, FUNCTION, AND METABOLISM IN LIVING SUBJECTS.

THESE ADVANCES REPRESENT ONLY A FEW OF THE MANY RECENT ACHIEVEMENTS WHICH ARE THE OUTGROWTH OF THE REVOLUTION IN BIOMEDICAL RESEARCH. TODAY, A MAJOR CHALLENGE FACING THE SCIENTIFIC COMMUNITY AS A WHOLE IS TO BUILD ON THESE ADVANCES, TO MAINTAIN THE CAPACITY OF THE NATIONAL BIOMEDICAL RESEARCH ENTERPRISE, AND TO SUSTAIN MOMENTUM IN A TIME OF CHANGES IN ORGANIZATIONAL PATTERNS AND IN THE FACE OF FISCAL RESTRAINTS.

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REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

STRICTLY SPEAKING, WE ARE NOT ONLY CELEBRATING THE 35TH ANNIVERSARY OF THE ESTABLISHMENT OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, WE ARE ALSO CELEBRATING THE 35TH BIRTHDAY OF THE NATIONAL INSTITUTES OF HEALTH. THE SAME ACT THAT CREATED THE NATIONAL HEART INSTITUTE NOTED THAT THE NATIONAL INSTITUTE OF HEALTH WOULD NO LONGER BE AN APPROPRIATE NAME AND ORDAINED THE PRESENT PLURAL FORM.

THE CREATION OF THE NATIONAL HEART INSTITUTE WAS ALSO A SIGNIFICANT EVENT IN THE EMERGENCE OF THE FEDERAL GOVERNMENT AS A PRINCIPAL PATRON OF HEALTH-RELATED RESEARCH. PRIOR TO WORLD WAR II, GOVERNMENTAL SUPPORT AND ACTIVITY IN THE BIOSCIENCES HAD BEEN MODEST. PRIVATE PHILANTHROPY WAS THE PRINCIPAL SOURCE OF FUNDING. UNDER THE PRESSURES OF WAR, ACADEMIC INSTITUTIONS AND EXISTING PRIVATE LABORATORIES HAD BEEN PROVIDED SUBSTANTIAL SUPPORT FOR CARRYING OUT MILITARILY RELATED BIOMEDICAL RESEARCH. DURING DEMOBILIZATION, THE EXISTING GOVERNMENT CONTRACTS AND GRANTS WERE TURNED OVER TO THE NATIONAL INSTITUTE OF HEALTH FOR ADMINISTRATION AND WHAT MIGHT HAVE BEEN A QUIET LIQUIDATION.

BUT THE WARTIME LESSONS ON THE PUBLIC BENEFITS OF RESEARCH WERE COMPELLING. THE ADMINISTRATION AND THE CONGRESS NO LONGER VIEWED FEDERAL SUPPORT OF BIO-MEDICAL RESEARCH JUST AS AN EMERGENCY MEASURE--BUT AS AN IMPORTANT FUNCTION OF GOVERNMENT FOR THE CURRENT AND FUTURE WELLBEING OF THE AMERICAN PEOPLE. IT WAS IN THE FORMATIVE PERIOD OF THE NEW NATIONAL POLICY THAT THE HEART INSTITUTE WAS AUTHORIZED.

IT IS NOT LIKELY THAT THE SPONSORS OF THE FOUNDING LEGISLATION FULLY ANTICIPATED HOW LARGE AND INFLUENTIAL THE NEW INSTITUTE WOULD BECOME.

IN THE INTERVENING YEARS, THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE HAS CONTRIBUTED GREATLY TO THE STORE OF KNOWLEDGE USED FOR THE SAVING OF THOUSANDS UPON THOUSANDS OF LIVES, AND FOR THE IMPROVEMENT OF THE QUALITY OF LIFE FOR MANY MORE THAN THAT. IN ADDITION, THE WHOLE OF SCIENTIFIC MEDICINE OWES MUCH TO THE CONTINUED VIGOR, EXCELLENCE, AND RIGOR OF NHLBI INTRAMURAL RESEARCH PROGRAMS, FOR THEY NURTURED AN UNUSUAL NUMBER OF LEADING INVESTIGATORS AND SCIENCE ADMINISTRATORS.

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*Words of Welcome for the NHLBI 35th Anniversary Celebration, ACRF Amphitheatre, September 21, 1983.

**Director, National Institutes of Health.

SO I CAN SAY WITH CONFIDENCE TO THE CURRENT ADMINISTRATORS, SCIENTISTS AND STAFF OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE THAT YOU AND YOUR PREDECESSORS HAVE AMPLE REASON INDEED TO PAUSE AND LOOK BACK WITH SATISFACTION TO 35 YEARS OF UNIQUE ACCOMPLISHMENT.

JUST MATCHING THESE ACCOMPLISHMENTS IN THE NEXT 35 YEARS IS, TO SAY THE LEAST, A CHALLENGING ASSIGNMENT, BUT I KNOW THAT YOU ASK OF YOURSELVES AND OF THOSE WHO WILL FOLLOW, YET MORE.

OPPORTUNITIES IN SCIENCE AND TECHNOLOGY FOR WOMEN, MINORITIES AND THE HANDICAPPED*

by

JAMES B. WYNGAARDEN, M.D.**

NIH, THROUGH RESEARCH AWARDS TO UNIVERSITIES, MEDICAL SCHOOLS AND OTHER INSTITUTIONS, AND IN ITS OWN LABORATORIES, IS COMMITTED TO SUPPORTING THE VERY BEST FUNDAMENTAL AND APPLIED BIOMEDICAL RESEARCH FOR THE ULTIMATE BENEFIT OF ALL PEOPLE. BASIC SCIENTIFIC KNOWLEDGE IN BIOLOGY AND MEDICINE IS EXPANDING AT AN AWESOME RATE, AND THE NEXT DECADE SHOULD SEE MANY VERY EXCITING DEVELOPMENTS IN SCIENCE AND MEDICINE.

ALTHOUGH FINANCIAL SUPPORT FOR BIOMEDICAL RESEARCH HAS CEASED TO GROW AND HAS ENTERED A NEW, STEADY STATE, WE HAVE AFFIRMED OUR EMPHASIS ON TAPPING THE BEST AND MOST CREATIVE INVESTIGATOR-INITIATED RESEARCH IDEAS AND ON KEEPING THE DOOR OPEN FOR NEW INVESTIGATORS JUST ENTERING THE POOL. THROUGH A ROSTER OF TRAINING PROGRAMS, NIH STRIVES TO ASSURE A CONTINUING SUPPLY OF WELL-TRAINED SCIENTISTS TO MEET THE NEEDS OF THE FUTURE.

NIH HAS LONG RECOGNIZED THE BENEFITS THAT CAN ACCRUE FOR THE HEALTH OF THE NATION AND THE STATE OF BIOMEDICAL SCIENCE IF THERE IS OPPORTUNITY FOR PARTICIPATION BY ALL MEMBERS OF SOCIETY, INCLUDING WOMEN, MINORITIES, AND THE HANDICAPPED. NIH HAS BEEN VERY AGGRESSIVE, ESPECIALLY IN THE PAST DECADE, IN ESTABLISHING CREATIVE PROGRAMS TO BRING THESE GROUPS—INCLUDING BLACKS, HISPANICS, ASIANS, AND NATIVE AMERICANS--INTO BIOMEDICAL SCIENCE. NO DOUBT, THERE ARE MANY MORE POSSIBILITIES TO EXPLORE FOR THE FUTURE, AND WE ARE CONSTANTLY EVALUATING OUR PROGRAMS AND ENTERTAINING NEW IDEAS TO ADDRESS THE UNDERREPRESENTATION OF THESE GROUPS IN THE NATIONAL BIOMEDICAL SCIENCE ENTERPRISE.

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* Address, Congressional Black Caucus Legislative Weekend, Rayburn Building, Washington, D.C. September 23, 1983.

** Director, National Institutes of Health

NIH'S TWO MAJOR PROGRAM EFFORTS TO INCREASE PARTICIPATION OF RACIAL AND ETHNIC MINORITIES IN NIH-SUPPORTED RESEARCH ARE THE MINORITY BIOMEDICAL RESEARCH SUPPORT PROGRAM (OR MBRS) OF THE DIVISION OF RESEARCH RESOURCES, AND THE MINORITY ACCESS TO RESEARCH CAREERS PROGRAM (OR MARC) OF THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES.

IN ITS EFFORT TO STRENGTHEN THE BIOMEDICAL CAPABILITIES OF MINORITY INSTITUTIONS, THE MBRS PROVIDES A RANGE OF OPPORTUNITIES: FOR FACULTY TO INITIATE RESEARCH; FOR UNDERGRADUATES TO PARTICIPATE IN FACULTY RESEARCH PROJECTS; AND FOR UPGRADING RESEARCH LABORATORIES IN MBRS INSTITUTIONS. CURRENTLY, ABOUT 610 FACULTY MEMBERS, 904 UNDERGRADUATES, AND 328 GRADUATE STUDENTS ARE PARTICIPATING WITHIN 74 INSTITUTIONS IN 25 STATES. TOTAL SUPPORT FOR FY 1982 WAS $24.6 MILLION (INCLUDING CO-FUNDING FROM ADAMHA).

WE NOW SEE SOME ENCOURAGING SIGNS THAT THE INVESTMENT IN THIS PROGRAM--STARTED IN 1972--IS BEGINNING TO PAYOFF: FACULTY AND STUDENTS FROM MBRS-SUPPORTED INSTITUTIONS ARE MAKING MORE PRESENTATIONS AT SCIENTIFIC MEETINGS; ABOUT 40 PERCENT OF CURRENT MBRS GRADUATES CHOOSE TO GO ON TO GRADUATE SCHOOL; ANOTHER 40 PERCENT CHOOSE MEDICAL OR DENTAL SCHOOL; MOST OF THE REST ACCEPT JOBS RELATED TO HEALTH. SOME MBRS-SUPPORTED INVESTIGATORS HAVE RECEIVED NATIONAL ATTENTION. FOR EXAMPLE, STUDIES CHARACTERIZING IRREVERSIBLY SICKLED CELLS WILL HELP IN THE SEARCH FOR A CURE FOR SICKLE CELL ANEMIA; NEW ANTIHYPERTENSIVE DRUGS WITH FEWER SIDE EFFECTS HAVE BEEN DEVELOPED FROM WORK CONDUCTED BY ONE OF THE PROGRAM'S EARLIEST PH.D. GRADUATES. THIS MBRS PROGRAM ALSO SUPPORTS AN ANNUAL SYMPOSIUM--THE NATION'S LARGEST GATHERING OF MINORITY STUDENTS AND BIOMEDICAL SCIENTISTS--BRINGING TOGETHER NEARLY 2000 PERSONS EACH YEAR. THIS YEAR I HAD AN OPPORTUNITY TO SPEAK AT THE MEETING HELD HERE IN WASHINGTON AND I WAS IMPRESSED WITH THE ENTHUSIASM OF THE STUDENTS PRESENTING POSTER LECTURES AND THE VAST RANGE OF DISCIPLINES COVERED.

WITH REGARD TO THE FUTURE OF THE MBRS PROGRAM: JUST ABOUT TWO WEEKS AGO, NIH CALLED A MEETING OF NATIONAL ADVISORY COUNCIL MEMBERS, MBRS PROGRAMS DIRECTORS, MINORITY SCIENTISTS, AND OTHERS TO ASSESS THE STRENGTHS AND WEAKNESSES OF THE MBRS PROGRAM AND GATHER IDEAS ABOUT HOW TO ENHANCE THE EFFORT. QUESTIONS AND SUGGESTIONS RAISED AT THE MEETING WILL BE EXAMINED OVER THE NEXT YEAR WITH INPUT FROM THE AFFECTED COMMUNITY.

A SECOND MAJOR PROGRAM—THE FIRST COMPONENT OF WHICH WAS BEGUN IN 1972--IS THE MARC PROGRAM. IT ALSO SEEKS WAYS TO ENRICH AND IMPROVE THE RESEARCH ENVIRONMENT OF MINORITY INSTITUTIONS. THIS IS A DYNAMIC PROGRAM, WITH COMPONENTS ADDED IN 1975, 1977 AND 1981. THE MARC HONORS UNDERGRADUATE PROGRAM IS CONSIDERED EXTREMELY SUCCESSFUL, HAVING BEGUN WITH 29 AWARDS IN 1977 AND GROWING BY 1981 TO 426 STUDENTS IN 89 PROGRAMS. IN THE LAST REVIEW OF STUDENTS GRADUATED IN 1979 (THERE WERE 46 GRADUATES), 48 PERCENT ENTERED GRADUATE SCHOOLS AND 30 PERCENT PROFESSIONAL SCHOOLS.

A RECENTLY COMPLETED EVALUATION OF THE MARC FACULTY FELLOWSHIP PROGRAM INDICATES THAT IT HAS HELPED SIGNIFICATNLY IN ENABLING FACULTY OF MINORITY INSTITUTIONS TO OBTAIN THEIR PH.D. DEGREES OR TAKE POSTDOCTORAL RESEARCH TRAINING. MANY OF THE FELLOWSHIP RECIPIENTS HAVE RETURNED TO THEIR HOME INSTITUTIONS, HAVE BECOME INVOLVED IN THE HIGHER LEVEL COMPONENTS OF THE MARC PROGRAM, AND HAVE OBTAINED RESEARCH GRANT SUPPORT FROM THE NIH AND ELSEWHERE. THE PROGRAM CAN CLAIM AMONG ITS GRADUATES FIVE DEPARTMENT CHAIRMEN, THREE ASSISTANT DEANS OR VICE CHANCELLORS, TWO ASSISTANT DEANS, AND ONE DIRECTOR OF A RESEARCH FOUNDATION. AN ADDITIONAL, IMPORTANT SPIN-OFF FOR THE GRADUATES OF THE PROGRAM IS THE OPPORTUNITY TO ESTABLISH PROFESSIONAL CONTACTS OUTSIDE THEIR CUSTOMARY ACADEMIC CIRCLES. A NUMBER HAVE BEGUN COLLABORATIVE RESEARCH PROJECTS WITH SCIENTISTS AT SOME OF THE LEADING BIOMEDICAL RESEARCH-INTENSE INSTITUTIONS IN THE COUNTRY.

ANOTHER SMALLER PROGRAM, BUT ONE THAT WE THINK HAS HAD AN IMPACT, IS THE EXTRAMURAL ASSOCIATES PROGRAM, DESIGNED NOT FOR SCIENTISTS BUT FOR RESEARCH ADMINISTRATORS AT MINORITY INSTITUTIONS. THIS PROGRAM PROVIDES THE OPPORTUNITY TO LEARN NOT ONLY ABOUT THE NIH EXTRAMURAL PROGRAMS, BUT ALSO TO BECOME FAMILIAR WITH OTHER AGENCIES IN THE WASHINGTON AREA THAT SUPPORT RESEARCH. GRADUATES OF THE PROGRAM RETURN TO THEIR INSTITUTIONS AFTER A FIVE-MONTH EXPERIENCE WITH REFERENCE MATERIALS AND SUFFICIENT UNDERSTANDING OF HOW NIH OPERATES SO THAT THEY CAN SERVE AS INVALUABLE LOCAL RESOURCES. THESE ASSOCIATES TEND TO KEEP UP THEIR INTERACTIONS WITH NIH STAFF LONG AFTER THEY HAVE LEFT THE PROGRAM.

I MENTIONED EARLIER THAT NIH STRIVES TO SUPPORT THE VERY BEST INVESTIGATOR-INITIATED RESEARCH PROJECTS, AND THE KEY MECHANISM TO SELECTION IS OF MINORITIES AND WOMEN ON THESE REVIEW PANELS (SOME 2,000 OR SO INDIVIDUALS) TO AT LEAST MATCH THE POOL STRENGTH IN THE FIELD OF BIOMEDICINE--A LEVEL OF ABOUT 23% FOR WOMEN AND 17% FOR MINORITIES. BECAUSE OF OUR OUTREACH PROGRAMS, THE PERCENTAGE

OF WOMEN ON OUR COMMITTEES ROSE FROM 2.9% TO 24% FROM 1971 TO 1981, AND THE PERCENTAGE OF MINORITIES ROSE FROM 3.4% TO 18.7% IN THE SAME TIMEFRAME. BUT, WE CANNOT AFFORD TO RELAX OUR EFFORTS IN THIS AREA. THE COMPOSITION OF OUR COMMITTEES IS CONSTANTLY MONITORED BY A COMPUTERIZED SYSTEM SO THAT ANY GAPS IN PARTICIPATION BY WOMEN OR MINORITIES CAN BE REVIEWED. ALL APPOINTMENTS TO COMMITTEES ARE REVIEWED BY THE OFFICE OF THE DIRECTOR, AND PROGRAM MANAGERS MUST JUSTIFY THEIR SELECTIONS. IF IT IS DETERMINED THAT THERE SIMPLY ARE NO WOMEN OR MINORITY SCIENTISTS AVAILABLE IN A PARTICULAR AREA OF SCIENCE, THEN THIS IS A CLUE TO US THAT MORE TRAINING IS REQUIRED IN THAT FIELD.

IN MY VIEW, NIH SHOWS UNIFORMLY A STRONG COMMITTMENT BY MANAGERS THROUGHOUT TO ADVANCE EQUAL OPPORTUNITY IN BIOMEDICINE. MANY COMPONENTS HAVE GENERATED THEIR OWN SUCCESSFUL PROGRAMS. FOR EXAMPLE, OVER THE PAST FIVE YEARS, THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES HAS BROUGHT IN ABOUT 100 OF THE COUNTRY'S BRIGHTEST BIOLOGY AND CHEMISTRY STUDENTS (AT LEAST HALF OF WHICH ARE FROM ETHNIC OR RACIAL MINORITY GROUPS) FOR SUMMER RESEARCH EXPERIENCES AT NIH'S OWN LABORATORIES. IT IS HOPED THAT THIS EARLY EXPOSURE TO RESEARCH WILL STIMULATE THE STUDENTS TO CONTINUE THEIR STUDIES AND EVENTUALLY LEAD THEM TO CAREERS IN BIOMEDICAL SCIENCE.

THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE HAS DEVELOPED THE MINORITY HYPERTENSION RESEARCH DEVELOPMENT SUMMER PROGRAM TO ENCOURAGE RECRUITMENT AND DEVELOPMENT OF MINORITY INVESTIGATORS IN RESEARCH, PREVENTION, CONTROL AND EDUCATION ACTIVITIES IN HYPERTENSION--A DISEASE WHICH IS MORE COMMON IN CERTAIN MINORITY POPULATIONS THAN IN WHITE POPULATIONS.

AN IDEA CONCEIVED BY AN INTRAMURAL SCIENTIST IN THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT IS BECOMING AN IMPORTANT COMMITMENT FOR INTRAMURAL SCIENTISTS NIH-WIDE. THIS YEAR ABOUT 100 TOP-LEVEL NIH SCIENTISTS HAVE SIGNED UP AS NIH VISITING PROFESSORS TO SPEND TIME AT MINORITY INSTITUTIONS GIVING SCIENTIFIC LECTURES, COUNSELING STUDENTS ON CAREER OPPORTUNITIES, AND CONFERRING ON RESEARCH PROJECTS.

I HAVE GIVEN A BRIEF OVERVIEW OF THE NIH EFFORTS TO INCREASE THE PARTICIPATION OF UNDERREPRESENTED GROUPS IN THE CONDUCT OF BIOMEDICAL RESEARCH. VIGILANCE IN EVALUATING OUR PROGRAMS AND PROGRESS WILL HELP US TO IMPROVE OUR RESULTS AND I BELIEVE THAT A CONTINUING DISCUSSION IS ESSENTIAL.

JUST THIS SUMMER I MET WITH THE SCIENCE ADVISORY COMMITTEE OF THE NATIONAL ASSOCIATION FOR EQUAL OPPORTUNITY IN HIGHER EDUCATION AND HAVE ASSURED THEM OF OPEN DISCUSSION ON ALL MATTERS AFFECTING THAT KEY SEGMENT OF THE BIOMEDICAL SCIENCE COMMUNITY. IN ADDITION, I APPRECIATE THE OPPORTUNITY TO MEET WITH THIS GROUP, AND WELCOME YOUR SUGGESTIONS AS WELL.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

MR. CHAIRMAN, PRESIDENT MASLAND, MADAME SECRETARY, LADIES AND GENTLEMEN, IT IS MY PLEASURE ON BEHALF OF THE NATIONAL INSTITUTES OF HEALTH TO JOIN IN WELCOMING YOU TO THE 15th EPILEPSY INTERNATIONAL SYMPOSIUM. FROM THE PROGRAM IT APPEARS THAT YOU WILL HAVE A VERY BUSY AND PRODUCTIVE WEEK AHEAD OF YOU.

THE NATIONAL INSTITUTES OF HEALTH IS THE FEDERAL AGENCY WITH PRIMARY RESPONSIBILITY FOR CONDUCTING AND FUNDING HEALTH RESEARCH. ABOUT FOUR-FIFTHS OF THE ANNUAL BUDGET OF THE NATIONAL INSTITUTES OF HEALTH, CURRENTLY $4 BILLION, IS USED TO SUPPORT SCIENTISTS DOING RESEARCH IN LABORATORIES OTHER THAN OUR OWN.

ON THE CAMPUS-LIKE GROUNDS IN BETHESDA, NIH MAINTAINS HUNDREDS OF LABORATORIES CONTAINING HIGHLY SOPHISTICATED RESEARCH EQUIPMENT, A 540-BED RESEARCH HOSPITAL, THE WARREN GRANT MAGNUSON CLINICAL CENTER, AND THE NATIONAL LIBRARY OF MEDICINE, THE WORLD'S LARGEST REPOSITORY OF MEDICAL LITERATURE, AND A NATIONAL CENTER FOR BIOMEDICAL COMMUNICATION. I HOPE THAT YOU WILL AVAIL YOURSELF OF THE OPPORTUNITY TO VISIT THESE FACILITIES DURING YOUR STAY IN WASHINGTON.

WITHIN NIH, AMONG THE 11 INSTITUTES AND SEVERAL OPERATING DIVISIONS, THE NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE IS PRIMARILY RESPONSIBLE FOR EPILEPSY RESEARCH. HOWEVER, SEVERAL OF THE OTHER COMPONENTS OF THE NATIONAL INSTITUTES OF HEALTH ALSO PERFORM RESEARCH RELATED TO EPILEPSY.

FOR EXAMPLE, THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES INCLUDES IN ITS RESEARCH PROGRAMS STUDIES ON INFECTIONS OF THE BRAIN. THIS INSTITUTE HAS SUPPORTED A SERIES OF PROJECTS TO DEVELOP VACCINES AGAINST THE MANY AGENTS THAT CAN CAUSE MENINGITIS. THE SUCCESSFUL DEVELOPMENT OF SUCH VACCINES WILL BE AN IMPORTANT ADVANCE IN THE PREVENTION OF MANY CASES OF LIFELONG EPILEPSY.

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*Opening Ceremony of the Fifteenth International Symposium on Epilepsy, Washington Hilton Hotel, September 26, 1983.

**Director, National Institutes of Health.

AT THE NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, MANY PROGRAMS RELATE TO THE PREVENTION OF EPILEPSY, PARTICULARLY TO THE PREVENTION OF EPILEPSY DUE TO INJURY TO THE NERVOUS SYSTEM DURING THE PRENATAL PERIOD, AND TO EPILEPSY CAUSED BY CONGENITAL MALFORMATION, BY BRAIN INJURIES IN INFANCY AND CHILDHOOD, AND BY LEAD POISONING.

THE NATIONAL INSTITUTE OF DENTAL RESEARCH SPONSORS STUDIES TO DETERMINE THE MECHANISM BY WHICH ANTICONVULSANT DRUGS CAUSE, AS ONE SIDE EFFECT, SEVERE GUM AND DENTAL PROBLEMS. WE SEEK TECHNIQUES FOR TREATING AND/OR PREVENTING THIS PROBLEM.

THE FOGARTY INTERNATIONAL CENTER AT THE NATIONAL INSTITUTES OF HEALTH HAS DEVELOPED FELLOWSHIPS TO SUPPORT RESEARCH BY FOREIGN SCIENTISTS IN THE UNITED STATES. THERE ARE SPECIAL EMPHASIS FELLOWSHIPS IN EPILEPSY. IN ADDITION, THE FOGARTY CENTER SUPPORTS INTERNATIONAL SYMPOSIA, WORKSHOPS, AND CONFERENCES; SOME OF THESE HAVE FOCUS ON ASPECTS OF EPILEPSY RESEARCH.

GREAT STRIDES HAVE BEEN MADE IN THE PAST DECADE TOWARD UNDERSTANDING THE CAUSES OF EPILEPSY AND TOWARD DEVELOPING IMPROVED TECHNIQUES FOR PREVENTION, DIAGNOSIS, TREATMENT, AND SEIZURE CONTROL. THERE REMAIN, HOWEVER, MANY PROBLEMS THAT ONLY FURTHER RESEARCH WILL SOLVE. WE ARE CONFIDENT THAT BASIC AND CLINICAL RESEARCH, SUCH AS THAT SUPPORTED BY THE NATIONAL INSTITUTES OF HEALTH, WILL LEAD TO A BETTER UNDERSTANDING OF THE DISORDER AND IMPROVED CARE FOR THE MILLIONS OF PERSONS AFFLICTED WITH SEIZURES.

YOU HAVE MY BEST WISHES FOR AN OUTSTANDING SYMPOSIUM.

# # # #

CURRENT LEGISLATIVE ISSUES THAT HAVE AN IMPACT ON NIH*

by

James B. Wyngaarden, M.D.**

There are a number of legislative issues in which NIH is interested, and probably a dozen or more bills pending in Congress at anyone time which have some potential impact on NIH. To keep this part of the Forum somewhat limited in time, I have selected just three issues which I think are of particular general interest and which are likely to have a significant impact on NIH.

The topics I will cover are NIH reauthorization legislation, animal welfare legislation, and congressional interest in and legislation related to Acquired Immune Deficiency Syndrome. I believe that these topics will illustrate both the broad span of Congressional interest in NIH programs and the direction of very specific interest in which the Congress seems to be heading.

REAUTHORIZATION

Historical

- o Reauthorization of programs with time-limited legislative authority is the one legislative issue which confronts NIH on a regular basis.

- o Prior to 1965, all funds for NIH research, research training, and information dissemination programs were appropriated under the broad legislative authority of Section 301 of the Public Health Service Act, enacted in 1944. This authority to conduct and support research and research training relevant to the cause, treatment, and prevention of human disease and to disseminate information about that research was not time limited. Section 301 is a section of the law which we have held sacred and which we continue to believe is extremely important. The general and permanent authority of Section 301 illustrates an historical understanding by the Congress - a somewhat rare and unusual understanding - of the unique nature of biomedical research as a long-term venture. In drafting Section 301, Congress reflected the fact that research does not fit in to the same mold as short-term programs conducive to mandatory periodic reauthorization. (SLIDE) This slide shows some other permanent NIH authorities, in addition to Section 301.

- o The first time-limited authority came in the 1965 Medical Library Assistance Act, which authorized the extramural programs of the National

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**Director, National Institutes of Health, Bethesda, Maryland.

Library of Medicine for a specific time period. (SLIDE) This slide shows all of the NIH time-limited authorites.

- The National Cancer Act of 1971 first authorized funds for an NIH research program for a specific time period.

- The 1972 National Heart, Blood Vessel, Lung, and Blood Act authorized the programs of the then National Heart and Lung Institute for a limited time.

- These laws initiated the current practice of requiring periodic renewal of authorities for some NIH activities. The reason for doing this was probably not exactly the same in each case. However, it undoubtedly reflected congressional desire for better control over certain kinds of programs, as well as constitutents' desire for more opportunity to appeal to the Congress for increased funding of programs in which they had special interest.

- Throughout the process of adding time and dollar limits, Congress never failed to remember and acknowledge that Section 301 is the fundamental authority and mandate for NIH research programs. Descriptions of institute and activities continued to be elaborations and specifications of Secion 301. Legislative language reminded us of this by including in every description the words "to carry out the purposes of Section 301."

- The National Research Act of 1974 went beyond the setting of time and dollar limits by actually eliminating research training authority in Section 301 and elsewhere in the law and placing exclusive legislative authority for research training in the new provisions. Today, the National Research Service Awards program is authorized under Section 472 of the Public Health Service Act. This authorization will expire on September 30. In fact, appropriations bills recently passed by the House and pending before the Senate make specific note of the fact that no funds are included for NSRA's because the program is not authorized.

- Besides NCI, NHLBI, the NRSA program, and the Medical Library Assistance Program, several NIADDK activities also have "time-and-dollar limits." They include diabetes and arthritis centers; arthritis demonstration projects; arthritis and diabetes data systems; and the arthritis, diabetes, and digestive diseases advisory boards.

- The centers, demonstration projects, and data systems can receive funds because they fall under the general research authority of Section 301. By contrast, the NIADDK Boards are not covered by Section 301.

- Other current basic statutory authorities in the PHS Act are shown on this SLIDE.

Current Status

- o I'm sure almost everyone here is aware of the fact that for the past five years we have had no appropriations bill but have operated under a series of Continuing Resolutions. Interestingly, for about the same period of time, the House and Senate authorizing committees have been unable to agree on a piece of authorizing legislation either. In 1980, there was ultimately a compromise between Sentor Kennedy and Representative Waxman which resulted in a simple reauthorization of expiring programs. Both had introduced bills which called for much more sweeping changes at NIH, both bills had been debated at length, and in the end no combination of the features of those bills could satisfy all parties. This apparent trend continued into subsequent Congresses. Senator Hatch and Representative Waxman sponsored quite different NIH legislation in the 97th Congress, and ultimately no bill was passed. We are faced with a similar situation this year.

- o Two bills, one each in the Senate and the House, are currently pending. Both have been considered by their respective committees of jurisdiction, and both are awaiting floor action.

- o The Senate bill, introduced by Senator Orrin Hatch of Utah, Chairman of the Senate Committee on Labor and Human Resources, has three major features. Its primary focus is reauthorization of our expiring programs. Secondly, there are some additional provisions, most of which are reasonable, although there is one major change recommended - that is, the establishment of a separate National Institute of Arthritis and Musculoskeletal and Skin Diseases. Third, the Senate bill is accompanied by exhortatory Report language.

- o Some of the provisions of this bill, other than reauthorization, are: requirement that National Advisory Councils be kept apprised of any investigations of possible scientific misconduct; requirement that we report to the Congress on how we are improving our review and awards process; and several task forces and reports designed to urge a greater NIH focus on such things as Alzheimers disease and spinal cord injury research.

- o The Senate bill very carefully avoids restrictive language. However, the Report accompanying the bill indicates some particular concerns of the Committee: They are

  --increasing incidence of scientific misconduct,
  --inequities and inefficiency in the peer review system,
  --inadequate focus on health promotion and disease prevention, and
  --inadequate research in rare diseases.

- o The Report also expresses a hope that consultation with NIH will solve problems more effectively than statutory changes, but warns that if desired results are not achieved by the next reauthorization, revisions of Titles III and IV may be needed.

- S. 773 has not yet been scheduled on the Senate calendar. There are several obstacles in its path. The most significant seems to be that Senator Packwood has placed a "hold" on the bill, preventing the bill from going to the Senate floor unless it is guaranteed that no amendment regarding fetal research will be offered. A "hold" is simply a request by one Senator that a particular bill not be scheduled on the Senate business calendar. Senator Packwood has made such a request, stating that he will object to having the bill brought to the Senate floor. Without Senator Packwood's consent, the Senate leadership will hold S. 773 back from Senate consideration. Therefore, immediate Senate Action on S. 773 seems unlikely.

- When we testified on S. 773 in March, we noted our support for the approach of this bill in reauthorizing our programs without proposing numerous major changes in our structure or system of operating. Of course, we opposed the creation of a new arthritis institute.

- The House reauthorization bill, H.R. 2350, introduced by Representative Henry Waxman contrasts sharply with the Senate version. Basically, it too contains three components, but its approach is far more detailed. The bill provides reauthorization of our expiring programs, but also provides new authorizations for a number of other activities. Secondly, in addition to establishing a new arthritis institute, the bill makes a number of other organizational changes at NIH. Finally, H.R. 2350 completely rewrites and revises Title IV of the Public Health Service Act and in so doing makes a number of very specific management and administrative requirements.

- Some of the new authorizations are for prevention centers, bioengineering centers, and mental retardation centers and research in spinal cord regeneration, alternatives for animal research methods, and Alzheimer's disease. The total amount authorized for these activities, some of which NIH carries out now but without special "earmarks" or legislative directives, is nearly $178 million.

- The bill also establishes 10 new committees, commissions, or task forces including interagency committees on spinal cord injury, learning disabilities, and Alzheimers disease; a National Commission on Orphan Diseases; and a President's Commission on Human Applications of Genetic Engineering.

- Among the organizational changes required at NIH would be the transfer to NIH of the National Center for Health Statistics, the National Center for Health Services Research, and the National Institute for Occupational Safety and Health.

- Some of the significant management and administrative requirements of the bill are listed on this slide. (SLIDE)

- A major potential impact of the Waxman bill relates to our use of the general research authority in Section 301 of the PHS Act. H.R. 2350 deletes all cross-references to Section 301 throughout the institute

descriptions in Title IV. The bill also deletes Section 478 of Title IV, a section which specifically allows the use of other legislative authorities, as needed, and, in particular, allows use of Section 301 as a "fallback" authority for our time-limited activities.

- The Report accompanying H.R. 2350 explains that Title IV, as revised by this bill, should be the exclusive authority for NIH activities and for appropriations for those activities. It states the Committee's view that Section 301 is "an unnecessary and duplicative authority" and that it is not to "be used as an authority for the appropriation or obligation of funds that could otherwise be appropriated...under Title IV."

- This is a radical departure from the long-standing historical precedent of Section 301.

- In the absence of enacted authorizing legislation, Congress has always been able to appropriate funds for our time-limited research programs based on the general Section 301 authority.

- Mr. Waxman's determination that Section 301 is not needed is as great a concern as the numerous special activities and the very specific management instructions in H.R. 2350.

- The importance of a basic, general authority such as Section 301 is illustrated by the recent appropriations actions with respect to the NRSA program. Funds for NRSA's are specifically omitted from FY 1984 Appropriations bills of the House and Senate, because the legislation to reauthorize that program has not passed. If Section 301 authority is eliminated, it is theoretically possible that other NIH programs could face this same kind of uncertainty in the appropriations process.

- The Administration has strongly opposed H.R. 2350 both in testimony before Represenative Waxman and in a letter from the Secretary stating our concerns that the bill attempts to legislate the management, organization, and scientific program priorities of NIH.

- When H.R. 2350 debate began on the House floor on July 25, Republican Representatives James Broyhill and Edward Madigan announced their intention to amend H.R. 2350 by introducing an "amendment in the nature of a substitute." The effect of such an amendment is to strike the entire content of the proposed bill and replace it with the language of the amendment.

- On September 14, that amendment was published in the Congressional Record. It is sponsored by Representatives Richard Shelby, a Democrat from Alabama, James Broyhill, and Edward Madigan. It contains provisions to reauthorize our expiring programs at funding levels equal to those in H.R. 2350, establish an arthritis institute, and establish and support prevention centers.

- o A Statement of Administration Policy, issued July 25, expressed support for the amendment, noting that it would be preferable to H.R. 2350. However, the statement expressed reservation about the funding levels and establishment of an arthritis institute.

- o When that policy statement was issued, we were not aware that prevention centers would be included in the amendment. Whether the Administration will revise its position remains to be seen.

- o Final House action on H.R. 2350 has not yet been scheduled. Reportedly, because of possible growing support for the substitute, Mr. Waxman wants to ascertain the chances of passage before bringing the bill to the floor for amendment and the House vote.

Conclusions

While the disagreement continues among members of Congress as to the best approach to NIH reauthorization, I suppose we can hope that the historical approach will prevail. That approach reflects what I believe is the only way to look at biomedical research - as a uniquely long-term process which holds as many disappointments as pleasant surprises, and in which it is almost never possible to predict long in advance where, when, or in what precise way we will find the answers we seek.

ANIMAL LEGISLATION

- o There is a long-standing Congressional concern about the welfare of research animals, but this concern has been bolstered in the last several years by increasing pressure from a multitude of public interest groups who have become increasingly vocal and powerful. This has resulted in a number of bills introduced in this Congress, relating to the care, treatment, and use of research animals.

- o One of the more controversial issues raised during Subcommittee and Committee consideration of H.R. 2350 related to provisions about the use of animals in research. Three separate provisions now appear in the bill: requirements that NIH promulgate guidelines for the care, treatment, and use of animals and for the operation of animal care committees at NIH-funded institutions; that a research plan be developed and research be supported in so-called "alternatives" to animal research methods; and that NIH arrange for a study of the use of animals in research.

- o S. 773, the Senate NIH bill, also requires a study of the use of animals in research.

- o S. 657, introduced by Senator Dole, amends the USDA-enforced Animal Welfare Act in several ways:

  --requirement that the Secretary of Agriculture upgrade some current USDA standards for care and treatment of research animals;

biomedical research and in the moral imperative to use those animals appropriately.

AIDS

o Let me now turn to an issue which has recently sparked enormous Congressional interest which has had a direct impact on the appropriation of funds for specific biomedical research, especially here at NIH. That issue is the disease Acquired Immune Deficiency Syndrome (AIDS).

General Information About AIDS and the NIH Role in Research on AIDS

o AIDS was first reported to the Centers for Disease Control in the spring of 1981. The NIH Clinical Center admitted its first AIDS patient for treatment shortly thereafter on June 16, 1981. Since that time, the disease has affected over 2200 persons and is progressing at an alarming rate. With this in mind, the NIH has accelerated its activities, both intramural and extramural, in an effort to solve the mystery. NIH intramural scientists have focused their attentions on both basic and clinical research in a concerted effort to attack the disease from a number of scientific bases. Through our extramural programs, we have supported the investigators nationwide whose research might lead to the identification of the causative agent and its mode of transmission, as well as prevention and treatment strategies for AIDS.

Appropriations Hearings-Specific Allocation of Funds Earmarked for AIDS (Supplemental)

o Congressional interest in AIDS was fully apparent during the annual appropriations hearings held in April of this year, where institute directors were asked a number of pointed questions about NIH activities related to AIDS, and especially about the degree of emphasis NIH is placing on the AIDS issue. Up to this point, no additional funds had been appropriated by the Congress for the specific purpose of supporting research on AIDS. Rather, funds had been reprogrammed from already existing programs and redirected to AIDS research efforts. Subsequent to these budget hearings, both the House and the Senate passed supplemental appropriations bills, which contained funds earmarked for AIDS research. The President signed the legislation in July, thus making an additional $9.4 million available to four NIH institutes for AIDS research. Another $3 million were allocated to other PHS agencies for the support of AIDS-related research. These funds may be obligated in either FY 1983 or 1984.

Problems of Earmarked Funds

o The earmarking of funds for AIDS research through Congressional action precludes the use of those funds for any purpose but that which was mandated. This earmarking of funds generally presents a special concern--in such cases, the agency is essentially forced to spend funds in specific areas regardless of the degree of scientific opportunity in that

area. In the case of AIDS research, we anticipate that the funds allocated through this special Congressional initiative will be well spent. A number of meritorious proposals for both clinical and basic research have been identified which will no doubt increase our understanding of, and ability to prevent or treat AIDS.

Reauthorization Hearings

- Not only have the Appropriations Committees been interested in AIDS, but the authorizing Committees have also shown interest in this area. During the NIH reauthorization hearing before the House Energy and Commerce Subcommittee on Health and the Environment, Representative Waxman raised a number of questions about NIH support of research on AIDS. These questions were directed primarily at the adequacy of NIH support of AIDS research and to the timeliness of our response to this public health problem.

Bills to Date on AIDS and Public Health Emergency Issues

- Interest in the AIDS issue and the ability of the Federal Government to respond to public health emergencies such as AIDS has resulted in the introduction of a number of bills in the 98th Congress. As of mid August, 12 bills related either specially to AIDS or to public health emergencies in general had been introduced in the House and Senate. Provisions calling for special review and award processes for research in public health emergencies are included in both the House and Senate NIH reauthorization bills.

- In addition, on July 13 the President signed the Public Health Emergency Fund Act, P.L. 98-49, which authorizes funds for the NIH, FDA, CDC, and ADAMHA for the conduct or support of research in the cause, prevention, or treatment of a declared public health emergency such as AIDS.

- The most recent activity was an August 1-2 AIDS Hearing before the House Government Operations Subcommittee on Intergovernmental Relations and Human Resources. Dr. Brandt, accompanied by representatives from CDC and NIH, addressed a number questions pertaining to the adequacy of Federal research efforts and the timeliness of our response. NIH is currently involved in responding to a number of questions raised by the Committee as a result of this hearing.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

THIS OCCASION IS A FIRST FOR ME--THE FIRST TIME I HAVE HAD THE OPPORTUNITY TO PRESENT THE DIRECTOR'S AWARDS AS WELL AS THE SPECIAL EEO ACHIEVEMENT AWARDS THAT WILL BE GIVEN TODAY.

IT IS ALSO THE FIRST TIME I HAVE HAD THE CHANCE TO MEET WITH BROAD REPRESENTATION OF THE NIH COMMUNITY WHEN I WAS NOT ACTING AS HOST FOR A VISITING DIGNITARY OR INVOLVED IN SOME SPECIAL OBSERVANCE. IN THOSE SITUATIONS, IT DID NOT SEEM QUITE APPROPRIATE FOR ME TO SAY SOME OF THE THINGS THAT I WANT TO EXPRESS TODAY.

IN THIS HONOR AWARDS CEREMONY, ALMOST 40 OUTSTANDING INDIVIDUALS WILL RECEIVE RECOGNITION FOR THEIR SIGNIFICANT CONTRIBUTIONS TO OUR COMMON EFFORT.

JUST GOING OVER THE NOMINATIONS WAS A GRATIFYING EXPERIENCE. I WAS REMINDED ANEW OF THE WIDE RANGE OF OCCUPATIONAL, TECHNICAL, AND PROFESSIONAL SKILLS REQUIRED FOR THE OPERATION OF THE NIH. BUT I WAS ESPECIALLY IMPRESSED BY THE RICH EVIDENCE IN THE NOMINATIONS ATTESTING TO THE SENSE OF PURPOSE--THE DEDICATION--AND THE EXPERTISE SHOWN BY NIH PERSONNEL ACROSS THE OCCUPATIONAL SPECTRUM.

IT IS A COMMON ERROR IN A SETTING LIKE THE NIH TO LIMIT THE DEFINITION OF "EXCELLENCE" AND TO MEASURE EXPERTISE BY AN INDIVIDUAL'S OUTPUT OF SCHOLARLY PAPERS. CERTAINLY SUCH PRODUCTIVITY IS IMPORTANT--IT IS AT THE HEART OF OUR MISSION--BUT OTHER FORMS OF EXCELLENCE THAT DO NOT FIT THE CRITERIA FOR WIDELY PUBLICIZED AWARDS ARE EQUALLY AS ESSENTIAL TO THE SUCCESS OF OUR EFFORTS. IN PART, IT WAS TO RECOGNIZE SUCH ACCOMPLISHMENTS THAT THE NIH DIRECTOR'S AWARD WAS ESTABLISHED.

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*Director's Award Ceremony, Masur Auditorium, September 29, 1983.

**Director, National Institutes of Health.

I DO NOT THINK IT DETRACTS IN ANY WAY FROM THE HONORS EARNED BY TODAY'S AWARDEES FOR ME TO SAY THAT, IN A REAL SENSE, THEY ARE REPRESENTATIVE OF MANY OTHERS, FOR ALL AROUND US ARE NIH WORKERS WHO MEET THE CRITERIA FOR THE DIRECTOR'S AWARD AS A RECOGNITION OF SUPERIOR PERFORMANCE OR SPECIAL EFFORTS SIGNIFICANTLY BEYOND THE REGULAR DUTY REQUIREMENTS.

PERMIT ME TO MENTION JUST TWO EXAMPLES: THE FIRST CONCERNS OVER 200 MEMBERS OF THE PROFESSIONAL AND SUPPORT STAFF OF THE DIVISION OF RESEARCH GRANTS. THEY HAVE JUST COMPLETED THE FIRST ROUND OF A MOST DIFFICULT AND DEMANDING TASK--REVIEW OF THE 1983 SMALL BUSINESS GRANTS APPLICATIONS. IN ORDER TO SET THIS NEW CONGRESSIONALLY MANDATED PROGRAM IN MOTION, IT WAS NECESSARY TO ESTABLISH NEARLY IMPOSSIBLE DEADLINES AND TO CALL ON MANY DRG PERSONNEL TO ACCEPT EXTRA RESPONSIBILITIES WHEN THEY WERE ALREADY CARRYING A HEAVY WORK LOAD. TO DO THE JOB REQUIRED A HIGH DEGREE OF FLEXIBILITY BECAUSE THE REQUIREMENTS OF THE SMALL BUSINESS INNOVATION RESEARCH PROGRAM REVIEW DID NOT FIT THE NORMAL PATTERNS OF WORK FLOW. BUT IT WAS DONE, AND IN ACCORD WITH THE HIGH STANDARDS WE HAVE COME TO EXPECT OF OUR PEER REVIEW PROCESS.

OTHER UNITS OF THE NIH WERE ALSO INVOLVED IN THIS SUCCESSFUL EFFORT. TO ALL WHO HAD A PART IN IT, I WISH TO EXPRESS MY APPRECIATION.

MY SECOND EXAMPLE INVOLVES THE VERY LARGE NUMBER OF NIH PERSONNEL, AS WELL AS SOME NON-NIH WORKERS, WHO WORKED LONG AND HARD TO ENSURE THAT THE AGENCY, PARTICULARLY THE CLINICAL CENTER, COULD CONTINUE TO FUNCTION IN THE FACE OF THE NEAR-BLIZZARD LAST FEBRUARY. WE ALL OWE SPECIAL THANKS TO THE CLINICAL CENTER STAFF WHO ASSURED UNINTERRUPTED PATIENT CARE; TO THE GROUNDS MAINTENANCE AND HOUSEKEEPING STAFFS WHO PLOWED AND SHOVELED OVER LONG PERIODS OF TIME TO CLEAR AND KEEP CLEAR OUR WALKS AND ROADS; TO THE GSI CAFETERIA EMPLOYEES WHO STAYED IN BUILDING 10 TO FEED THE STAFF OVER THE SNOWBOUND WEEKEND; TO THE POLICE AND FIREMEN WHO HELPED STRANDED MOTORISTS; AND TO THE MAINTENANCE ENGINEERS WHO STAYED ON THE JOB LONG AFTER THEIR SHIFTS HAD ENDED.

WHILE OTHER EXAMPLES OF SUCH CARING AND UNSELFISH SERVICE DID NOT INVOLVE SUCH LARGE NUMBERS WORKING TOGETHER, THERE ARE MANY OTHER ACCOMPLISHMENTS OF THE PAST YEAR EQUALLY AS WORTHY OF THE THANKS OF ALL OF US.

TODAY WE WILL ALSO RECOGNIZE IMPORTANT ACHIEVEMENTS IN PROMOTING THE AIMS OF THE EQUAL OPPORTUNITY PROGRAM AND IN STRENGTHENING THIS VITAL PROGRAM WHOSE QUALITY AND SUCCESS ARE MEASURES OF OUR COMMITMENT TO THE GOALS OF EQUITY AND ACTIVE CONCERN FOR OTHERS.

I AM GLAD TO HAVE THIS OPPORTUNITY TO EXPRESS MY PERSONAL APPRECIATION TO EVERY MEMBER OF THE NIH FAMILY AND TO EXTEND MY WARMEST CONGRATULATIONS TO THOSE AMONG YOU WHO WILL RECEIVE THE SPECIAL RECOGNITION SO RICHLY DESERVED.

* * * *

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

PLACING THE NAME OF GLEN MORROW ON THIS SURGICAL SUITE IMPOSES AN OBLIGATION ON ALL WHO USE IT. IT IS A REMINDER TO CONTINUE THE RESTLESS SEARCH FOR KNOWLEDGE, TO APPLY THAT KNOWLEDGE WITH CONSUMMATE SKILL AND COMPASSION, AND TO TEACH GENEROUSLY BUT RIGOROUSLY. AND ALL THIS SEARCHING--THIS SERVING--THIS TEACHING MUST BE DONE WITH TREMENDOUS ENTHUSIASM IF THE PRESENCE OF GLEN MORROW IN THIS PLACE IS TO BE FULLY EXPRESSED.

IN ANOTHER PART OF THIS BUILDING, THERE IS AN INSCRIPTION THAT WOULD BE SINGULARLY APPROPRIATE HERE. ENGRAVED ON A MARBLE PANEL AT THE ENTRANCE OF THE AUDITORIUM NAMED FOR HIM IS A QUOTATION FROM JACK MASUR. ALTHOUGH THE WORDS REFER TO THE ENTIRE HOSPITAL FACILITY, THEY APPLY WITH SPECIAL MEANING TO THE MORROW DOMAIN--APTLY DESCRIBING IN A FEW WORDS THE QUALITY AND INDIVISIBILITY OF HIS COMMITMENT. "HOSPITALS WITH LONG TRADITIONS OF EXCELLENCE," DR. MASUR SAID, "HAVE DEMONSTRATED ABUNDANTLY THAT RESEARCH ENHANCES THE VITALITY OF TEACHING, TEACHING LIFTS THE STANDARDS OF SERVICE, AND SERVICE OPENS NEW AVENUES OF INVESTIGATIONS."

ALTHOUGH IN MY FIRST AND RELATIVELY BRIEF TOUR AT NIH IT WAS NOT MY PRIVILEGE TO WORK CLOSELY WITH DR. MORROW, THE SENSE OF ADVENTURE THAT HE GENERATED IN HIS ASSOCIATES AND TRAINEES SWEPT OVER ALL OF US. THEY WORKED HARD AND ENJOYED IT. ALMOST EVERYTHING THEY DID WAS BEING DONE FOR THE FIRST TIME AND THIS PIONEERING LED BY GLEN MORROW PLACED A MORAL STAMP OF HIGH SPIRITS ON ALL WHO WORKED WITH HIM.

ALMOST AN ENTIRE GENERATION OF THE FINEST AND BRIGHTEST OF AMERICA'S CARDIOVASCULAR SURGEONS BEAR INDELIBLY THE MORROW STAMP, FOR MANY OF THEM WERE TRAINED HERE OR, AT SOME POINT IN THEIR EARLY CAREER, WORKED WITH THIS MAN AND SHARED THE EXCITEMENT AND KNOWLEDGE HE GENERATED.

AT A TIME WHEN MOST BLAYLOCK-TRAINED SURGEONS WERE ATTRACTED TO LUCRATIVE POSTS IN MEDICAL SCHOOLS OR IN PRIVATE PRACTICE, GLEN MORROW MADE THE DECISION TO DEDICATE HIS WEALTH OF TALENT TO RESEARCH AND TO THIS PLACE. UNCOUNTED NUMBERS HAVE BEEN THE DIRECT BENEFICIARIES OF THAT DECISION WHOSE SALUTARY EFFECT WILL OUTLAST ALL OF US WHO HAVE COME HERE TO EXPRESS OUR GRATITUDE FOR IT.

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*Glen Morrow Dedication Ceremony, Clinical Center Surgical Wing, September 30, 1983.

**Director, National Institutes of Health.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

I AM TOLD THAT A FEW YEARS AGO THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE ANNOUNCED THAT NO SENIOR OFFICIAL SHOULD STAY IN THE SAME JOB FOR MORE THAN FIVE YEARS BECAUSE, AFTER THAT TIME, ADMINISTRATORS LOSE VISION AND DRIVE. ALL I CAN SAY FROM PERSONAL OBSERVATION IS THAT IF MARTY SLOWED DOWN DURING HIS NINETEENTH AND TWENTIETH YEARS AS DIRECTOR OF THE NATIONAL LIBRARY OF MEDICINE, HE MUST HAVE BEEN ONE OF THE WONDERS OF THE WORLD IN THE SIXTIES AND SEVENTIES. THE FACT IS, AS ALL OF YOU KNOW, HIS RELENTLESS DEVOTION TO MAKING AND KEEPING THE NATIONAL LIBRARY OF MEDICINE PREEMINENT IN THE WORLD HAS NOT DIMINISHED--RATHER IT HAS INTENSIFIED.

AT THE TIME OF HIS RETIREMENT AS DIRECTOR OF NLM, MARTY HAD BY FAR THE LONGEST TENURE IN A MAJOR POSITION OF ANY OF THE PRINCIPAL OFFICIALS AT NIH.

IN THAT JOB, HE SERVED CONTEMPORANEOUSLY WITH ELEVEN DEPARTMENTAL SECRETARIES, SEVEN ASSISTANT SECRETARIES OF HEALTH, FIVE SURGEONS GENERAL, AND FIVE DIRECTORS OF NIH. YOU MAY HAVE NOTICED THAT I SAID HE SERVED "WITH" THOSE 28 PEOPLE. THE QUESTION AS TO WHO SERVED "UNDER" WHOM IS AN ISSUE THAT HAS NEVER BEEN FULLY RESOLVED.

HIS ABLE, FIERCE AND UNCONDITIONAL DEVOTION TO THE ORGANIZATION HE HAS HEADED IS AN EXEMPLIFICATION OF THE BEST BEST IN FEDERAL SERVICE. MORE IMPORTANTLY, MARTY'S ACCOMPLISHMENTS WILL HAVE A LASTING AND BENEFICIAL EFFECT ON SCIENCE, THE PRACTICE OF MEDICINE, AND THE HEALTH OF THE PEOPLE EVERYWHERE.

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*Ceremony/reception, retirement of Dr. Martin Cummings, Director, National Library of Medicine, Lister Hill Center, October 7, 1983.

**Director, National Institutes of Health.

PROGRAM AND POLICY DIRECTIONS OF THE NATIONAL INSTITUTES OF HEALTH*

by

JAMES B. WYNGAARDEN, M.D.**

AT THE TIME DR. HANLON GRACIOUSLY INVITED ME TO GIVE THIS LECTURE, HE SENT ME A LIST OF THOSE WHO HAD PREVIOUSLY HAD THIS HONOR. IT IS AN IMPOSING ROSTER, INDEED. TO FOLLOW SUCH DYNAMIC FIGURES AS FRANCIS MOORE, SHERMAN MELLINKOFF, ROBERT MCNAMARA, AND NORMAN COUSINS IS, TO SAY THE LEAST, DAUNTING. JUST READING THE TITLES OF THE MOST RECENT ADDRESSES MAKES ME WISH I COULD HAVE HEARD THEM, SO THAT I COULD HAVE LEARNED WHAT, FOR EXAMPLE, HERBERT BOYER MEANT WHEN HE SAID, "EVEN GENETICISTS GET THE BLUES," OR HOW WILLARD GAYLIN APPROACHED THE SUBJECT OF "MODERN MEDICINE AND THE PRICE OF SUCCESS," TO WHICH HE ADDED AS A SUBTITLE THE PROVOCATIVE QUESTION, "AFTER ALL WE'VE DONE FOR YOU, HOW CAN YOU TREAT US THIS WAY?"

THE TITLE OF MY PRESENTATION, "PROGRAM AND POLICY DIRECTIONS OF THE NATIONAL INSTITUTES OF HEALTH," UNDENIABLY IS LESS SUBJECT TO INTERPRETATION THAN THE ONES I HAVE JUST MENTIONED. A STRICT CONSTRUCTIONIST, HOWEVER, MIGHT NOTE MY USE OF THE PLURAL FOR THE WORD "DIRECTIONS" AND ASK IF I AM IMPLYING THAT POLICY GOES ONE WAY AND PROGRAMS ANOTHER. I CERTAINLY HOPE NOT, ALTHOUGH I WILL CONFESS THAT AVOIDING SUCH DIVERGENCE SOMETIMES TAKES CONCENTRATED EFFORT.

I WAS INVITED TO GIVE THIS LECTURE AS THE RELATIVELY NEW DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH. I HAVE NOW BEEN IN THAT POSITION FOR A YEAR AND A HALF. IT HAS BEEN A TIME OF EXTRAORDINARY LEARNING FOR ME--HAPPIER NOT KNOWING ONE OF THE EARLY SURPRISES WAS THE INTENSITY OF THE INTERACTIONS BETWEEN A MULTITUDE OF SPECIAL INTEREST GROUPS AND THE NIH, AS WELL AS THE MEMBERS OF CONGRESS. SOMETIMES WASHINGTON SEEMS LIKE ONE HUGE MONOPOLY GAME -- "I'LL BUY TIMES BEACH IF YOU'LL SELL YOSEMITE PARK," OR "YOU VOTE FOR AWAK BOMBER SALES AND I'LL VOTE FOR THE SMALL BUSINESS SET-ASIDE." I NOW UNDERSTAND WHAT IS MEANT BY THE SAYING THAT THERE ARE TWO THINGS YOU DO NOT WANT TO KNOW HOW THEY ARE MADE. ONE IS SAUSAGE AND THE OTHER IS LEGISLATION.

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*American Urological Association Lecture at the 83 Clinical Congress of the American College of Surgeons, World Congress Center, Atlanta, Georgia, October 17, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

AS A CONSEQUENCE OF SOME OF MY EXPERIENCES, I HAVE BECOME A MARXIST--A GROUCHO MARXIST. GROUCHO OBSERVED, "EVERYONE IN GOVERNMENT IS CONSTANTLY LOOKING FOR PROBLEMS, FINDING THEM EVERYWHERE, MAKING THE WRONG DIAGNOSES, AND PROPOSING THE WRONG SOLUTIONS." IN CONSEQUENCE, MUCH OF WHAT I DO COULD BE CALLED "DAMAGE CONTROL." I HAVE TRACED THE ORIGINATOR OF THE SAM RAYBURN AXIOM, "IF IT'S NOT BROKE, DON'T FIX IT," TO KING LEAR, WHERE THE DUKE OF ALBANY PROTESTS--"STRIVING TO BETTER, OFT WE MAR WHAT'S WELL."

BUT IRRESPECTIVE OF THE PROCESS, MANY OF THE LAWS PASSED BY CONGRESS ARE WISE, VISIONARY, AND OF IMMENSE BENEFIT TO AMERICA'S PEOPLE AND INSTITUTIONS. I PLACE THE SUCCESSION OF LAWS THAT ESTABLISHED AND MOLDED NIH IN THAT CATEGORY. THE NIH-UNIVERSITY PARTNERSHIP IS A UNIQUE AMERICAN SUCCESS STORY, ONE THAT HAS BEEN EXTRAORDINARILY PRODUCTIVE IN RESEARCH DISCOVERY AND ADVANCEMENT OF HEALTH, ONE THAT HAS BROUGHT THE UNITED STATES INTERNATIONAL PRESTIGE. THE ACCOMPLISHMENTS OF THIS JOINT ENDEAVOR HAVE BENEFICIALLY TOUCHED THE LIVES OF MOST PEOPLE DIRECTLY OR INDIRECTLY AND PROMISE EVEN MORE FOR THE FUTURE.

EVEN A CURSORY EXAMINATION OF THE FACTS AND FIGURES DESCRIPTIVE OF THIS PARTNERSHIP GIVES AN IMPRESSIVE PICTURE OF ITS MAGNITUDE AND SIGNIFICANCE TO AMERICAN SCIENCE.

THE FEDERAL GOVERNMENT SUPPORTS AN ESTIMATED 90 PERCENT OF BASIC BIOMEDICAL RESEARCH IN THIS COUNTRY. MORE THAN 60 PERCENT OF SUCH RESEARCH AND DEVELOPMENT AT AMERICAN UNIVERSITIES AND MEDICAL SCHOOLS IS FUNDED BY ONE FEDERAL AGENCY--THE NATIONAL INSTITUTES OF HEALTH.

IN THE CURRENT FISCAL YEAR, NIH EXPENDITURES IN GRANTS AND CONTRACTS FOR RESEARCH AND TRAINING WILL AMOUNT TO WELL OVER THREE BILLION DOLLARS, REPRESENTING ABOUT 78 PERCENT OF OUR TOTAL BUDGET. ABOUT HALF OF OUR AWARDS WILL GO TO MEDICAL SCHOOLS, A PROPORTION THAT HAS RUN BETWEEN 49 AND 52 PERCENT SINCE 1975.

MORE THAN 1,200 INSTITUTIONS, INCLUDING ALL OF THE COUNTRY'S MAJOR UNIVERSITIES, 122 MEDICAL SCHOOLS, AND MANY TEACHING HOSPITALS CARRY OUT RESEARCH AND TRAINING SUPPORTED BY NIH.

THE LATEST COUNT OF THE NUMBER OF SALARIED POSITIONS SUPPORTED BY NIH GRANTS WAS MADE IN 1978. AT THAT TIME, A TOTAL OF 102,953 POSITIONS WERE FUNDED THROUGH OUR EXTRAMURAL GRANTS. OF THESE RESEARCH POSITIONS, 47,980 WERE OCCUPIED BY PROFESSIONAL LEVEL SCIENTISTS--THE LARGEST PORTION BEING ACADEMIC FACULTY MEMBERS. BUT, OF COURSE, THE STRENGTH OF OUR PARTNERSHIP IN RESEARCH IS DETERMINED BY THE QUALITY RATHER THAN THE QUANTITY OF THE SCIENTISTS INVOLVED.

BY ANY CRITERION, THE PROGRAMS OF THE NIH ENLIST THE CREAM OF AMERICAN SCIENTISTS.

FOR EXAMPLE, OF THE 36 AMERICANS NAMED AS NOBEL LAUREATES IN PHYSIOLOGY OR MEDICINE OVER THE PAST 25 YEARS, 30 OR 83 PERCENT OF THEM EITHER HAD WORKED AT THE NIH OR HAD BEEN SUPPORTED IN THEIR ACADEMIC SETTING BY THE NIH BEFORE BEING AWARDED THE PRIZE.

ANOTHER DIMENSION OF OUR JOINT ENDEAVOR RELATES TO THE TRAINING OF FUTURE SCIENTISTS. ALMOST 10,000 POSTDOCTORAL TRAINEES AT ACADEMIC INSTITUTIONS THROUGHOUT THE COUNTRY ARE BEING SUPPORTED THROUGH OUR TRAINING PROGRAMS.

FINALLY, I WANT TO CITE ANOTHER FACET OF THAT RELATIONSHIP, THE ROLE OF THOUSANDS OF AMERICAN SCIENTISTS AS RESPONSIBLE ADVISORS AT PRACTICALLY EVERY LEVEL OF NIH RESEARCH ACTIVITIES, PARTICULARLY THE PART THEY PLAY IN REVIEWING RESEARCH PROPOSALS.

AT LEAST THREE TIMES EACH YEAR, SOME 2,000 SENIOR SCIENTISTS COME TO BETHESDA AS MEMBERS OF THE 99 INITIAL REVIEW GROUPS TO EXAMINE, DISCUSS, AND EVALUATE THE MORE THAN 20,000 GRANT PROPOSALS WE RECEIVE ANNUALLY. MANY OF YOU IN THE AUDIENCE SERVE OR HAVE SERVED IN THIS CAPACITY. THE CONSIDERED OPINIONS OF OUR ADVISORS ARE CRITICALLY IMPORTANT IN SELECTING THE PROJECTS TO BE FUNDED, BECAUSE IN RECENT YEARS WE HAVE BEEN ABLE TO SUPPORT ONLY A LITTLE MORE THAN ONE-THIRD OF THE ELIGIBLE PROJECTS.

MORE THAN EVER BEFORE, THE SEARCH FOR NEW BIOMEDICAL KNOWLEDGE IS INFLUENCED BY THE EXPERT JUDGMENTS OF OUR ADVISORS AS THEY RECOMMEND PRIORITIES FOR INDIVIDUAL PROPOSALS. WE ARE FORTUNATE TO HAVE ACCESS TO THIS TREMENDOUSLY VALUABLE RESOURCE. EQUALLY VALUABLE ADVISORY BODIES ASSIST US IN MANY OTHER ASPECTS OF NIH PROGRAMS, INCLUDING THE SUBSTANTIAL RESEARCH ACTIVITIES CONDUCTED IN-HOUSE.

AT THE HEART OF AN OBJECTIVE APPRAISAL OF THE FEDERAL-ACADEMIC PARTNERSHIP, HOWEVER, IS CONSIDERATION OF ITS EFFECT AS AN INSTRUMENT FOR INCREASING KNOWLEDGE FOR THE IMPROVEMENT OF HEALTH AND THE PREVENTION OF DISEASE. HAS IT WORKED?

I WILL STATE THE OBVIOUS. BIOMEDICAL SCIENCE IN THIS COUNTRY AND ELSEWHERE HAS EXPERIENCED A VERITABLE EXPLOSION OF KNOWLEDGE THAT PROMISES A FURTHER CASCADE OF NEW DISCOVERIES. THE FEDERAL-ACADEMIC PARTNERSHIP HAS BEEN A MAJOR FORCE IN THE SPECTACULAR EXPANSION OF THE FRONTIERS OF KNOWLEDGE.

SINCE THE 1940s, THE PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH HAVE CONSTITUTED A PRIME EXPRESSION OF FEDERAL POLICY ON BIOMEDICAL RESEARCH IN THE UNITED STATES. AS SHAPED BY SUCCESSIVE ADMINISTRATIONS AND THE CONGRESS, THAT POLICY HAS FROM THE BEGINNING ENCOURAGED DIVERSITY AND EXCELLENCE IN HEALTH RESEARCH; IT HAS RELIED ON THE SCIENTIFIC COMMUNITY ITSELF TO IDENTIFY THROUGH A COMPETITIVE PEER REVIEW PROCESS THE IDEAS AND INVESTIGATORS MOST WORTHY OF SUPPORT.

OUR BROAD CHARTER IS CONTAINED IN SECTION 301 OF THE PUBLIC HEALTH SERVICE ACT OF 1944 WHICH CONTINUES TO BE OUR GOVERNING STATUTE. THE COMMITTEE REPORT THAT ACCOMPANIED THE ACT STATED THAT THE PURPOSE OF THE LEGISLATION WAS TO "CONSOLIDATE AND RESTATE THE BASIC AUTHORITY OF THE PUBLIC HEALTH SERVICE IN THE WHOLE FIELD OF RESEARCH SO AS TO GRANT IN CLEAR AND UNMISTAKABLE TERMS BROAD AUTHORITY TO CARRY ON INVESTIGATIONS THROUGH ITS OWN PERSONNEL AND TO COOPERATE AND ASSIST IN THE INVESTIGATION BY OTHERS OF ALL PROBLEMS BEARING ON THE PHYSICAL AND MENTAL HEALTH OF OUR PEOPLE."

BY THE MID-FIFTIES, THE OVERALL BUDGET OF THE NIH HAD GROWN TO 82 MILLION, OF WHICH MORE THAN 54 MILLION WAS EXPENDED IN GRANTS. THE STAGE HAD BEEN SET FOR A RAPID AND MASSIVE EXPANSION OF NIH AND ITS PROGRAMS. DURING THE FOLLOWING DECADE, THE TOTAL NIH BUDGET GREW TWELVEFOLD AND EXPENDITURES FOR GRANTS FIFTEENFOLD.

THIS PERIOD OF SPECTACULAR GROWTH CAN BE VIEWED AS THE RESULT OF A FIRM ACCEPTANCE BY THE FEDERAL GOVERNMENT OF THE RESPONSIBILITY FOR SUPPORT OF BIOMEDICAL RESEARCH--BASIC RESEARCH IN PARTICULAR.

IT WAS FORTUNATE THAT DURING THE PERIOD OF ITS EXPLOSIVE GROWTH FROM 1955 TO THE LATE SIXTIES, THE NIH WAS DIRECTED BY AN UNUSUALLY ABLE, SENSITIVE, AND STRONG LEADER, DR. JAMES A. SHANNON. UNDER DR. SHANNON, MANY OF THE CURRENT MECHANISMS OF SUPPORT OF BIOMEDICAL SCIENCE WERE ESTABLISHED, CONFIRMED, AND EXTENDED. THEY HAVE SERVED THE NIH AND THE SCIENTIFIC COMMUNITY WELL. JIM SHANNON INSISTED THAT THE CONGRESSIONAL MANDATE TO CONDUCT RESEARCH IN CANCER, HEART DISEASE, AND ARTHRITIS, FOR EXAMPLE, BE INTERPRETED BROADLY. HE REALIZED THAT THE SCIENCE BASE WAS NOT SUFFICIENT TO PERMIT A FRONTAL ASSAULT ON THE DISEASES THEMSELVES. HE SET ABOUT TO BUILD THE RESEARCH CAPABILITY OF THIS COUNTRY THROUGH THE INTRAMURAL PROGRAM AT BETHESDA AND THROUGH A SUBSTANTIAL EXPANSION OF THE MECHANISMS OF GRANTS-IN-AID TO INSTITUTIONS.

COROLLARY OBJECTIVES INCLUDED THE STRENGTHENING OF THE INSTITUTIONS IN WHICH BIOMEDICAL RESEARCH WOULD BE DONE AND THE DEVELOPMENT OF TRAINING MECHANISMS THAT WOULD ENSURE A CONTINUING SUPPLY OF COMPETENT SCIENTISTS DRAWN FROM THE BRIGHTEST YOUNG MINDS IN THE UNIVERSITIES. TOGETHER WITH HILL BURTON MONEY FOR CLINICAL FACILITIES, NIH CONSTRUCTION FUNDS FOR RESEARCH FACILITIES MODIFIED THE TOPOGRAPHY OF ACADEMIC MEDICAL CENTERS AND INDIRECTLY GREATLY STRENGTHENED MEDICAL EDUCATION IN THIS COUNTRY.

FOR DECADES, THE MAIN NIH MECHANISM OF RESEARCH SUPPORT HAS BEEN INDIVIDUAL PROJECT GRANTS FOR STUDIES PROPOSED FOR NONGOVERNMENT SCIENTISTS. JUST OVER ONE-HALF OF THE NIH BUDGET CURRENTLY IS USED FOR THE SUPPORT OF SUCH INVESTIGATOR-INITIATED PROJECTS.

WITHOUT AN APPRECIATION OF THE SOCIOLOGY OF SCIENCE, ONE MIGHT QUESTION THE WISDOM OF MAKING THE INVESTIGATOR-INITIATED GRANT PROJECT THE KEYSTONE OF A NATIONAL RESEARCH EFFORT. IN USING THIS MECHANISM, WE ARE UTTERLY DEPENDENT UPON THE VOLUNTARY SUBMISSION BY INDIVIDUAL SCIENTISTS OF NEW RESEARCH IDEAS. IN ONE SENSE, IT IS THE FREE ENTERPRISE SYSTEM TAKEN TO THE EXTREME. THE NIH HAS LITTLE OR NO CONTROL OVER THE RANGE OR NATURE OF THE IDEAS SUBMITTED TO IT FOR POSSIBLE FUNDING. YET THIS VERY LACK OF CONTROL IS THE SOURCE OF THE AGENCY'S ABILITY TO TAP THE BEST IDEAS OF THE BEST MINDS IN THE NATION.

CERTAINLY NO ONE SCIENTIST, NO MATTER HOW SOPHISTICATED OR EXPERIENCED, NOR ANY PANEL OF DISTINGUISHED SCIENTISTS COULD HAVE THE INSIGHT AND CREATIVE ABILITY TO PRODUCE THE ARRAY OF RESEARCH PROPOSALS SUBMITTED TO THE NIH.

THE QUESTION MIGHT BE ASKED, "IF THE INVESTIGATOR-INITIATED GRANT IS SO PRODUCTIVE, WHY DOESN'T NIH DEVOTE ALL OF ITS FUNDS AVAILABLE FOR EXTRAMURAL RESEARCH TO THAT MECHANISM?" THE ANSWER IS THAT A NUMBER OF VITAL RESEARCH ACTIVITIES REQUIRE OTHER MECHANISMS; FOR EXAMPLE, LARGE CLINICAL TRIALS. USUALLY, THESE TRIALS ARE CONDUCTED SIMULTANEOUSLY AT A NUMBER OF CENTERS SPREAD ACROSS THE COUNTRY. TO ASSURE COMPARABILITY AND VALIDITY OF THE FINDINGS COMING FROM THE VARIOUS SOURCES, IT IS NECESSARY THAT A UNIFORM PROTOCOL BE RIGIDLY FOLLOWED AT EACH OF THE CENTERS. IN THIS INSTANCE, CREATIVE VARIATIONS FROM THE AGREED-UPON RESEARCH PLAN WOULD BE DESTRUCTIVE. SO THE USUAL MECHANISM FOR THE SUPPORT OF CLINICAL TRIALS IS A CONTRACT.

SPECIALIZED AND COMPREHENSIVE CENTERS REPRESENT ANOTHER MECHANISM FOR ACCOMPLISHING NIH'S PURPOSES. SUCH CENTERS SUPPORT RESEARCH ON THE CAUSES, PREVENTION, AND TREATMENT OF SPECIFIC DISEASES AND DEMONSTRATION OF NEW METHODS OF TREATMENT.

SUBSTANTIAL FUNDS ARE ALSO DEVOTED TO RESEARCH TRAINING. BECAUSE OF THE CENTRAL RELATIONSHIP OF TRAINING TO THE FUTURE OF BIOMEDICAL RESEARCH, I WILL IN A MOMENT DISCUSS IT AT GREATER LENGTH.

THERE IS ONE OTHER FRUIT OF THE NIH-ACADEMIC PARTNERSHIP THAT SHOULD BE MENTIONED. THE JOINT VENTURE HAS GREATLY STRENGTHENED THE UNIVERSITY IN SCIENCE TEACHING AND IN COMMUNITY SERVICE. THE AUDITORIUM IN OUR CLINICAL CENTER AT THE NATIONAL INSTITUTES OF HEALTH HAS A QUOTATION FROM THE FIRST DIRECTOR OF THE CENTER, DR. JACK MASUR, ENGRAVED IN THE MARBLE WALL AT ITS ENTRANCE THAT BEAUTIFULLY CAPTURES THIS CONCEPT. IT SAYS, "HOSPITALS WITH LONG TRADITIONS OF EXCELLENCE HAVE DEMONSTRATED ABUNDANTLY THAT RESEARCH ENHANCES THE VITALITY OF TEACHING, TEACHING LIFTS THE STANDARDS OF SERVICE, AND SERVICE OPENS NEW AVENUES OF INVESTIGATION." FOR HOSPITALS, ONE COULD EQUALLY WELL READ UNIVERSITIES OR MEDICAL SCHOOLS.

WHILE, AS I HAVE SAID, THE NIH IS ESSENTIALLY NON-DIRECTIVE WITH REGARD TO ITS EXTRAMURAL PROGRAMS, THERE ARE OCCASIONS WHEN WE ATTEMPT TO STIMULATE THE INTEREST OF INVESTIGATORS IN CERTAIN AREAS OF RESEARCH. RECENTLY WE ISSUED FORMAL REQUESTS FOR APPLICATIONS ON STUDIES RELATED TO ACQUIRED IMMUNE DEFICIENCY SYNDROME. MUCH OF THE IMMUNOLOGICAL RESEARCH WHICH WE HAVE SUPPORTED THROUGH THE PAST YEARS HAS A DIRECT BEARING ON THIS DISTURBING NEW PROBLEM AND FORMS AN IMPORTANT BASE FOR FURTHER STUDIES, BUT THERE IS AN URGENT NEED TO FOCUS ON THE PARTICULAR MANIFESTATIONS OF THE BREAKDOWN OF THE IMMUNE SYSTEM ASSOCIATED WITH AIDS. INTENSIVE EFFORT IS BEING DEVOTED TO THE PROBLEM OF IDENTIFYING THE CAUSATIVE AGENT OF AIDS AND THE POSSIBLE MEANS OF ITS TRANSMISSION, AND WE HAVE CALLED UPON THE RESEARCH COMMUNITY TO FOCUS ON THE PROBLEM AND TO SUBMIT NEW IDEAS FOR RESEARCH.

WITHIN THE LAST HALF CENTURY, THE AMERICAN PUBLIC HAS A NEW APPRECIATION OF THE IMPORTANCE OF RESEARCH. THAT PUBLIC CONFIDENCE AND LEVEL OF EXPECTATION HAS DEVELOPED BECAUSE GREAT PROGRESS IN EXPANDING THE BORDERS OF FUNDAMENTAL KNOWLEDGE HAS MADE IT POSSIBLE TO PROCEED TO THE DEVELOPMENT OF POWERFUL MEASURES FOR THE PREVENTION AND TREATMENT OF DISEASES. BUT THE BASE OF KNOWLEDGE MUST COME FIRST AND IT IS FOR THIS REASON THAT THE NIH CONTINUES ITS POLICY OF COMMITTING A LARGE SHARE OF ITS RESOURCES TO BASIC STUDIES.

BECAUSE PUBLIC AND PRIVATE FUNDS ARE NOT UNLIMITED, IT IS INCUMBENT ON ALL OF US TO ASSURE THAT SUPPORT IS GIVEN TO WORK OF THE HIGHEST QUALITY. IN A RECENT SPEECH ON FEDERAL RESEARCH AND DEVELOPMENT POLICY, THE PRESIDENT'S SCIENCE ADVISOR, GEORGE KEYWORTH, COMMENTING ON MAKING BETTER USE OF OUR NATION'S RESEARCH RESOURCES, STATED THAT "GOOD INTENTIONS AND KEEPING BUSY DO NOT COUNT, RESULTS DO. FOR THAT REASON," HE SAID, "OUR FIRST PRIORITY NOW IS TO PERMIT THE BEST RESEARCH TO BE MORE FULLY SUPPORTED SO THAT ITS INFLUENCE CAN BE

EXTENDED. THIS IS THE TIME TO DO A JOB WITH THE BEST TOOLS WE HAVE, NOT A TIME TO DISSIPATE OUR RESOURCES BY PARCELING THEM OUT IN RESPONSE TO POPULAR DEMAND."[1]

I HAVE SPOKEN OF HOW THE NIH IS DEPENDENT UPON THE NATION'S SCIENTIFIC COMMUNITY FOR THE EXPERTISE NEEDED IN MAKING CRITICAL JUDGMENTS AMONG THE COMPETING PROPOSALS THAT WE RECEIVE EACH YEAR.

CURRENTLY, MANY STRONG, POTENTIALLY PRODUCTIVE AND VALUABLE RESEARCH PROJECTS CANNOT BE FUNDED, AND EXCELLENT ESTABLISHED INVESTIGATORS, AS WELL AS WELL-QUALIFIED NEWCOMERS, ARE BEING DENIED SUPPORT BECAUSE OF THE STRINGENCY OF THE BUDGET. IT IS ONLY NATURAL AT SUCH A TIME THAT THE MECHANISM BY WHICH JUDGMENTS ARE MADE WOULD COME UNDER EXTERNAL PRESSURE. SOME SCIENTISTS HAVE ATTACKED THE FUNDAMENTAL INTEGRITY AND EQUITY OF THE PEER REVIEW SYSTEM.

IT IS A HUMAN SYSTEM AND NO ONE WOULD CONTEND THAT ITS JUDGMENTS ARE FLAWLESS. YET IT HAS OPERATED WITH VERY LITTLE CRITICISM FOR 30 YEARS AND WE CONTINUE TO HAVE THE STRONGEST CONFIDENCE IN ITS OVERALL PERFORMANCE.

THERE ALWAYS HAS BEEN A CUTOFF POINT BELOW WHICH GRANTS COULD NOT BE PAID DUE TO LIMITATION OF FUNDS. HOWEVER, THE DIFFERENCES IN QUALITY OF APPLICATIONS AT THE MARGIN ARE QUITE SMALL WHEN WE ARE ABLE TO PAY ONLY A LITTLE ABOVE ONE-THIRD OF THE QUALIFIED APPLICATIONS AS COMPARED WITH THE MARGINAL DIFFERENCES WHEN WE COULD FUND A HALF OR MORE OF THE WORTHY PROPOSALS. THE JUDGMENTS ARE MUCH MORE DIFFICULT, AND UNREST IN THE EXTRAMURAL COMMUNITY IS CORRESPONDINGLY HIGHER. THE ONLY WAY TO AVOID THE PROBLEM ALTOGETHER IS TO BE ABLE TO PAY ALL APPROVED GRANTS AND THIS UTOPIAN DAY IS UNLIKELY EVER TO ARRIVE. APPLICANTS WHOSE PRIORITY SCORES FALL OUTSIDE THE PAY LINE ARE PROVIDED INFORMATION ON THE SHORTCOMINGS OF THEIR APPLICATIONS AND HAVE THE OPTION OF REWRITING THEIR MATERIAL AND RESUBMITTING. LAST YEAR, ONE-FOURTH OF ALL APPLICATIONS WERE RESUBMISSIONS, A CATEGORY OF APPLICATIONS THAT HAS DOUBLED IN SIZE IN THE PAST THREE TO FIVE YEARS.

FOR THOSE OF US WHO, ONE WAY OR ANOTHER, HAVE HAD CONTACT WITH THE NIH OVER A PERIOD OF TIME, THESE SIGNS OF STRESS SHOULD COME AS NO SURPRISE. THE AGENCY WENT THROUGH A SPECTACULAR PERIOD OF GROWTH IN THE MID-FIFTIES AND EARLY SIXTIES BUT, OF COURSE, IT WOULD HAVE BEEN UNREALISTIC TO EXPECT THAT RATE OF GROWTH TO CONTINUE INDEFINITELY.

MANY OF US WERE BADLY SPOILED, PARTICULARLY THE GENERATION OF NOW SENIOR RESEARCH SCIENTISTS PRIVILEGED TO MATURE IN AN ERA MARKED BY REGULAR ANNUAL INCREASES IN THE FUNDS AVAILABLE TO SUPPORT OUR RESEARCH. THERE WERE, TO BE

SURE, A FEW JEREMIAHS WHO PROPHESIED THAT AN ANNUAL 15 PERCENT INCREASE IN THE RESEARCH BUDGET AND AN ANNUAL 3 TO 6 PERCENT INCREASE IN THE GROSS NATIONAL PRODUCT COULD NOT PERSEVERE INDEFINITELY. THOSE WHO ENJOYED SUCH MISCHIEF DELIGHTED IN IDENTIFYING THE YEAR WHEN THE ENTIRE FEDERAL BUDGET WOULD BE DIRECTED TOWARD SCIENTIFIC RESEARCH. YET WE BLITHELY WENT AHEAD ASSUMING THAT THE APPROPRIATION FOR SCIENTIFIC RESEARCH WOULD ALWAYS TAKE CARE OF OUR NEEDS. THE FAILING IS HUMAN. WE ALSO CONTINUE TO BEHAVE AS THOUGH OUR NATURAL RESOURCES ARE INEXHAUSTIBLE.

IN 1975, THE APPROPRIATION FOR THE NIH EXCEEDED THREE BILLION DOLLARS FOR THE FIRST TIME, BUT IN THE PAST DECADE THE GROWTH IN SUPPORT HAS BEEN MORE APPARENT THAN REAL.

THE 1979 APPROPRIATION OF 3.2 BILLION REPRESENTS AN ALL-TIME HIGH IN CONSTANT DOLLARS, BUT WAS WORTH ONLY 1.92 BILLION IN 1972 DOLLARS, AND BETWEEN 1979 AND 1982, THE FLOW OF CONSTANT DOLLARS FELL BY 12 PERCENT. A SLIGHT INCREASE IN THE 1983 BUDGET BRINGS THE 1972 CONSTANT DOLLAR LEVEL BACK TO 1.77 BILLION. THE HOUSE AND SENATE HAVE BOTH PASSED THE 1984 BUDGET. THEY ARE ABOUT EIGHT TO NINE MILLION DOLLARS APART, AND THE CONFERENCE TODAY (OCTOBER 17) IS CONSIDERING THIS 11% INCREASE WHICH WE THINK THE PRESIDENT WILL SIGN. THE INCREASES OF 1983 AND 1984 RETURNED THE NIH BUDGET ALMOST TO THE 1979 LEVEL.

(SLIDE 1)

IN SHORT, THE NIH BUDGET HAS BEEN ESSENTIALLY IN A STEADY STATE FOR MORE THAN A DECADE AND WE CANNOT EXPECT DRAMATIC INCREASES IN THE NEAR FUTURE, CERTAINLY NOT UNTIL THE NATIONAL ECONOMY IMPROVES. AT THE SAME TIME, BIOMEDICAL RESEARCH HAS RECEIVED STRONG SUPPORT FROM THE PRESENT AND PREVIOUS ADMINISTRATIONS AND CONGRESSES AND HAS FARED BETTER THAN MANY OTHER FIELDS, SUCH AS PHYSICS AND ENGINEERING, IN RECENT YEARS.

OVER THE PAST DECADE, NIH HAS BEEN ACCOMMODATING TO A RELATIVELY CONSTANT BUDGET AND HAS FUNDED AN INCREASING NUMBER OF EXCELLENT RESEARCH PROPOSALS BY SHIFTING FUNDS AMONG OUR VARIOUS PROGRAM MECHANISMS. THESE CHANGES BEGAN IN 1974 BUT WERE NOT ARTICULATED AS A POLICY UNTIL FISCAL YEAR '80 WHEN WE ASKED THE CONGRESS FOR SUFFICIENT FUNDS TO SUPPORT A MINIMUM OF 5,000 NEW AND COMPETING RESEARCH GRANTS AND 10,000 TRAINEES.

WE CONTINUE TO EMPHASIZE STABILITY IN THE RESEARCH PROJECT BASE BECAUSE PURSUIT OF FUNDAMENTAL KNOWLEDGE IS THE FOUNDATION OF PROGRESS IN THE HEALTH SCIENCES AND INVESTIGATOR-INITIATED RESEARCH HOLDS THE GREATEST PROMISE OF SIGNIFICANT DISCOVERY. OUR OBJECTIVE IS TO PROVIDE A STEADY AND PREDICTABLE

LEVEL OF RESEARCH PROJECT SUPPORT, ONE THAT OFFERS CONTINUITY TO ESTABLISHED INVESTIGATORS AND THAT ENCOURAGES NEW SCIENTISTS TO ENTER THE FIELD.

THE STABILIZATION POLICY HAS IN FACT DONE JUST THAT. WE HAVE BEEN ABLE TO DAMPEN LARGE FLUCTUATIONS IN SUPPORT OF NEW AND COMPETING RENEWAL AWARDS. IN 1981, WE SUPPORTED 5,109 SUCH GRANTS AND, IN 1982, 5,027. THESE GRANTS WERE IN ADDITION TO THE 11-12,000 CONTINUING GRANTS THAT CARRIED OVER FROM PREVIOUS YEARS. OUR AVERAGE GRANT IS AWARDED FOR A PERIOD OF THREE TO FOUR YEARS.

IN FY 1983 WHICH ENDED JUST 17 DAYS AGO, WE BEGAN THE YEAR EXPECTING TO BE ABLE TO AWARD 4,966 NEW AND COMPETING GRANTS. BUT BY THE YEAR'S END, MORE THAN 5,200 SUCH GRANTS WERE AWARDED, IN ADDITION TO 123 NEW GRANTS UNDER THE MANDATED SMALL BUSINESS INNOVATIVE RESEARCH PROGRAM. THESE ACTIONS ILLUSTRATE NIH'S DEEP COMMITMENT TO INVESTIGATOR-INITIATED RESEARCH FOR, TO ACHIEVE SUCH LEVELS, IT WAS NECESSARY TO SHIFT FUNDS FROM OTHER PROGRAMS.

HOWEVER, GIVEN FINITE RESOURCES AND A COMMITMENT TO STABILIZATION OF ONE GROWING ELEMENT AMONG SEVERAL NECESSARY ACTIVITIES, THE ULTIMATE RESULT IS DESTABILIZATION OF THE OTHERS. IN FACT, IF THE CURRENT RATE OF INCREASE IN THE PERCENTAGE OF THE NIH BUDGET DEVOTED TO THE EXTRAMURAL GRANT COMPONENT WERE TO CONTINUE, IT WOULD REACH 100 PERCENT AND PUSH ASIDE ALL OTHER ACTIVITIES BY AROUND 1993. OF COURSE, WE CANNOT PERMIT THAT TO HAPPEN.

LET US FOCUS FOR A MOMENT ON RESEARCH MANPOWER AND TRAINING. WE BELIEVE THAT TO ASSURE THE CONTINUED SUCCESS OF RESEARCH ACTIVITY, AN ACTIVE RESEARCH MANPOWER DEVELOPMENT PROGRAM MUST BE SUSTAINED FOR SELECT INDIVIDUALS AT ALL STAGES OF INTELLECTUAL AND PROFESSIONAL DEVELOPMENT. THIS UNDERLYING PHILOSOPHY WAS SUCCINCTLY STATED IN THE PREAMBLE TO THE CONGRESSIONAL ACT UNDER WHICH MANY OF OUR TRAINING PROGRAMS ARE CARRIED OUT. THE CONGRESS DECLARED THAT "(1) THE SUCCESS AND CONTINUED VIABILITY OF THE FEDERAL BIOMEDICAL AND BEHAVIORAL RESEARCH EFFORT DEPENDS ON THE AVAILABILITY OF EXCELLENT SCIENTISTS AND A NETWORK OF INSTITUTIONS OF EXCELLENCE CAPABLE OF PRODUCING SUPERIOR RESEARCH PERSONNEL; (2) DIRECT SUPPORT OF THE TRAINING OF SCIENTISTS FOR CAREERS IN BIOMEDICAL AND BEHAVIORAL RESEARCH IS AN APPROPRIATE AND NECESSARY ROLE FOR THE FEDERAL GOVERNMENT; AND (3) GRADUATE RESEARCH ASSISTANCE PROGRAMS SHOULD BE THE KEY ELEMENT IN THE TRAINING PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH."[2]

IN OUR VIEW, THE TRAINING AND RESEARCH PROGRAMS ARE SO CLOSELY INTERWOVEN AS TO BE PRACTICALLY INDIVISIBLE. AS A MATTER OF FACT, ALTHOUGH IN OUR DISCUSSIONS OF THE STABILIZATION INITIATIVE WE USUALLY MENTION ONLY THE NEED FOR AT LEAST 5,000 NEW AND COMPETING GRANTS, OUR STABILIZATION POLICY ALSO EXTENDS

TO THE GOAL OF AT LEAST 10,000 TRAINEES IN ACADEMIC INSTITUTIONS THROUGHOUT THE NATION.

THIS BOND BETWEEN TRAINING AND RESEARCH WAS ADDRESSED IN DR. KEYWORTH'S STATEMENT ON FEDERAL POLICY TO WHICH I REFERRED EARLIER IN THIS DISCUSSION. HE NOTED THAT "AS A GROUP, AMERICAN RESEARCH UNIVERSITIES ARE THE BEST IN THE WORLD BOTH IN TERMS OF PRODUCING THE NEW KNOWLEDGE THAT STIMULATES TECHNOLOGY AND IN TERMS OF PRODUCING THE PEOPLE WHO DRIVE THE INNOVATIVE PROCESS IN SOCIETY. THAT UNIQUE DUAL FUNCTION," HE SAYS, "EXPLAINS OUR TREMENDOUS EMPHASIS ON UNIVERSITY RESEARCH. NO OTHER RESEARCH INSTITUTIONS--FEDERAL LABORATORIES, NONPROFIT ORGANIZATIONS OR INDUSTRIAL LABORATORIES--GIVE SO MUCH IN RETURN ON INVESTMENT IN THE LONG TERM. NO OTHER INSTITUTIONS PRODUCE BOTH KNOWLEDGE AND PEOPLE."[3]

THE INTENSE COMPETITION FOR RESEARCH SUPPORT HAS INCREASINGLY TAKEN ITS TOLL OF THE AMATEUR OR UNDER-TRAINED INVESTIGATOR. THE PROFESSIONALIZATION OF RESEARCH ACTIVITY HAS PROGRESSIVELY SELECTED AGAINST THE M.D. SCIENTIST WHO 15 YEARS AGO HAD A MUCH BETTER PROSPECT OF SUCCESS IN RESEARCH APPLICATIONS THAN THE PH.D. APPLICANT. SINCE 1974, APPLICANTS HAVING BOTH THE M.D. AND PH.D. DEGREES HAVE ENJOYED THE HIGHEST SUCCESS RATE, FOLLOWED BY THOSE WITH PH.D.'s. THE M.D. SCIENTIST IS COMPETING STEADILY LESS WELL.

THE NATIONAL ACADEMY OF SCIENCES CONDUCTS A CONTINUING STUDY OF THE NATIONAL NEED FOR BIOMEDICAL AND BEHAVIORAL RESEARCH PERSONNEL. THE FINDINGS OF THE STUDY ARE USED BY THE NIH IN PLANNING FOR ITS RESEARCH TRAINING PROGRAM.

A MAJOR CONCERN OF THE ACADEMY AND ALSO OF THE NIH HAS BEEN A DECREASE IN THE NUMBER OF PHYSICIANS WHO ARE SEEKING RESEARCH TRAINING. THE ACADEMY RECOMMENDED THAT AT LEAST 2,800 INDIVIDUALS HOLDING THE M.D. OR EQUIVALENT DEGREE BE SUPPORTED UNDER THE ESTABLISHED RESEARCH TRAINING PROGRAM EVERY YEAR. THAT GOAL HAS NOT BEEN REACHED. AS A MATTER OF FACT, THERE HAS BEEN A CONSIDERABLE DECLINE IN THE NUMBERS OF PROFESSIONAL DEGREE HOLDERS UNDERTAKING RESEARCH TRAINING. WHILE THE ABSOLUTE NUMBER OF CLINICAL POSTDOCTORAL FELLOWS HAS LEVELED OFF TO A RELATIVELY CONSTANT NUMBER IN THE RANGE OF 1,900 PER YEAR SINCE 1976, IT FALLS FAR SHORT OF MEETING THE ACADEMY'S RECOMMENDATIONS.

(SLIDE 2)

THE APPLICATION OF SCIENTIFIC ADVANCES TO MAINTAIN GOOD HEALTH AND TO PREVENT AND TREAT DISEASE IS ULTIMATELY THE RESPONSIBILITY OF THE PHYSICIAN. THE TRAINED CLINICAL INVESTIGATOR IS THE CRITICAL LINK BETWEEN THE LABORATORY AND THE HEALTH CARE PROVIDER. IN THE FACE OF THE EXPLOSIVE GROWTH OF BASIC KNOWLEDGE IN THE BIOMEDICAL SCIENCES WHICH HAS OPENED UP VAST OPPORTUNITIES FOR

CLINICAL RESEARCH, THE SHORTFALL IN TRAINING OF CLINICAL INVESTIGATORS ASSUMES ADDITIONAL SIGNIFICANCE.

AMONG THE REASONS CITED FOR THE DECLINING INTEREST OF PHYSICIANS IN CLINICAL RESEARCH ARE THE FOLLOWING:

- o EXTRAORDINARY INCOMES ARE AVAILABLE IN PRACTICE ESPECIALLY IN THE PROCEDURE-ORIENTED SUBSPECIALTIES.

- o THE DEBT LOAD OF MEDICAL STUDENTS HAS GROWN ENORMOUSLY. WHILE THE AVERAGE IS ABOUT $19,000, DEBTS AS HIGH AS $30,000 UPON GRADUATION ARE NOT UNUSUAL.

- o THE NIH TRAINING STIPEND PAYS ON THE AVERAGE $6,000 PER YEAR LESS THAN DOES CLINICAL SPECIALITY TRAINING.

- o THE AVERAGE MEDICAL SCHOOL CURRICULUM CONTAINS LITTLE OR NO OPPORTUNITY FOR LABORATORY EXPERIENCE.

- o SPECIALTY TRAINING PROGRAMS HAVE LENGTHENED AND ARE QUITE RIGID WITH RESPECT TO INCLUSION OF RESEARCH TRAINING.

- o THE GROWING SOPHISTICATION OF SCIENCE AND ITS PROFESSIONALIZATION IN CLINICAL DEPARTMENTS REQUIRE THAT THE RECIPIENTS OF EVEN THE FINEST MEDICAL EDUCATION AND RESIDENCY TRAINING SPEND A SUBSTANTIAL AMOUNT OF ADDITIONAL TIME, AS LONG AS THREE YEARS, OBTAINING THE NECESSARY SKILLS TO BE SUCCESSFUL IN RESEARCH.

IN THE FACE OF THESE NEGATIVE FACTORS AND PARTLY TO COUNTER THEM, THE NIH HAS DEVELOPED SEVERAL PROGRAMS IN ADDITION TO ITS REGULAR RESEARCH TRAINING GRANTS THAT ARE DESIGNED TO ACQUAINT THE PHYSICIAN IN TRAINING WITH THE EXCITEMENT AND POSSIBILITIES OF BIOMEDICAL RESEARCH:

(1) BECAUSE MEDICAL CURRICULA TODAY HAVE ELIMINATED MANY OF THE LABORATORY EXERCISES THAT ONCE INTRODUCED STUDENTS TO RESEARCH EXPERIENCES, THE NIH HAS INITIATED A PROGRAM OF SHORT-TERM TRAINING IN HEALTH PROFESSIONAL SCHOOLS TO EXPOSE STUDENTS EARLY IN THEIR PROFESSIONAL STUDIES TO OPPORTUNITIES IN RESEARCH. THE PROGRAM NOW SUPPORTS MORE THAN 1,100 STUDENTS A YEAR DURING VACATION OR OFF-QUARTER PERIOD IN APPROXIMATELY 70 SCHOOLS OF MEDICINE, DENTISTRY, PHARMACY, AND VETERINARY MEDICINE.

(2) A SECOND PROGRAM PROVIDING AN EARLY RESEARCH EXPERIENCE IS A SUMMER FELLOWSHIP AT THE NIH OFFERED TO OUTSTANDING MEDICAL STUDENTS THROUGHOUT THE COUNTRY. LAST YEAR, 52 MEDICAL AND DENTAL STUDENT FELLOWS SELECTED FROM VARIOUS INSTITUTIONS CONDUCTED LABORATORY RESEARCH AND ATTENDED LECTURES AND SEMINARS AT NIH.

(3) A THIRD INITIATIVE FOR ATTRACTING MEDICAL STUDENTS INTO RESEARCH IS ONE OFTEN CALLED THE "POSTSOPHOMORE FELLOWSHIP." IT IS OUR VIEW THAT A SHORT-TERM EXPOSURE TO RESEARCH, ALTHOUGH USEFUL AS AN INTRODUCTION, IS LESS EFFECTIVE THAN A LONGER INITIAL LABORATORY EXPERIENCE. ACCORDINGLY, THE NIH IN THE SUMMER OF 1982 REESTABLISHED A PROGRAM FOR SUPPORT OF STUDENTS WHO INTERRUPT PROFESSIONAL EDUCATION FOR A FULL YEAR OF RESEARCH TRAINING.

(4) THE NEWEST ADDITION TO THE CAREER DEVELOPMENT AWARD PROGRAM, CALLED THE PHYSICIAN-SCIENTIST AWARD, WAS ANNOUNCED LAST JULY. THIS AWARD IS SUPPORTED BY SEVERAL OF THE NIH INSTITUTES. IT IS DESIGNED TO PROVIDE FIVE YEARS OF PHASED SUPERVISED RESEARCH TRAINING. THE FIRST FEW YEARS OF RESEARCH TRAINING WILL BE OBTAINED IN A BASIC SCIENCE DEPARTMENT. THE AWARD WILL CARRY A SALARY EQUIVALENT TO THAT EARNED BY A MEMBER OF THE INSTITUTION'S HOUSE STAFF WITH EQUIVALENT EXPERIENCE AND WILL INCLUDE $10,000 FOR RESEARCH COSTS. THE SECOND PHASE UNDERTAKEN AT A MORE INDEPENDENT LEVEL WILL HAVE UP TO $20,000 AVAILABLE TO COVER RESEARCH COSTS. AT THE CONCLUSION OF THIS FIVE-YEAR PROGRAM, A YOUNG PHYSICIAN-SCIENTIST SHOULD BE WELL PREPARED TO COMPETE FOR NIH RESEARCH GRANT SUPPORT.

(5) IN ADDITION, WE ARE CONTINUING TO GIVE TOP PRIORITY TO THE M.D., PH.D., OR MEDICAL SCIENTIST TRAINING PROGRAM.

OF COURSE, THERE ARE MANY OTHER CLINICAL RESEARCH TRAINING PROGRAMS CARRIED OUT AND FUNDED BY THE TEACHING INSTITUTIONS. FOR EXAMPLE, DUKE UNIVERSITY AND THE UNIVERSITY OF MINNESOTA HAVE LONG-STANDING COMBINATION SURGICAL RESIDENCY RESEARCH PROGRAMS WHERE SUBSTANTIAL AMOUNTS OF TIME DURING RESIDENCY ARE DEVOTED TO INTENSIVE TRAINING AND EXPERIENCE IN THE METHODOLOGY AND CONDUCT OF RESEARCH.

BUT THE WISDOM OF UNDERTAKING RESEARCH TRAINING COULD EASILY BE QUESTIONED BY A YOUNG PHYSICIAN IF THE OPPORTUNITY TO ENGAGE IN SUPPORTED RESEARCH IN THE FUTURE IS HIGHLY UNCERTAIN. ONE MAJOR FACTOR HAVING AN IMPACT UPON THE YOUNG PHYSICIAN'S DECISION IS HIS OR HER PERCEPTION OF THE LONG-TERM STABILITY OF FEDERAL SUPPORT OF RESEARCH. THIS IS ONE REASON FOR NIH'S CONTINUED EMPHASIS ON THE NEED TO "STABILIZE" OUR OFFERING OF GRANTS FOR INVESTIGATOR-INITIATED PROJECT RESEARCH--TO PROVIDE A REASONABLE DEGREE OF ASSURANCE ABOUT FUTURE

OPPORTUNITIES. THE POLICY OF FUNDING A MINIMUM OF 5,000 NEW AND COMPETING AWARDS HAS HELPED, WE BELIEVE, TO STABILIZE EMERGING RESEARCH CAREERS. CURRENTLY, 50 PERCENT OF NEW AWARDS AND 10 PERCENT OF ALL AWARDS ARE MADE TO FIRST-TIME APPLICANTS, NOT BY ALLOCATION, BUT ON THE BASIS OF OPEN COMPETITION.

ANOTHER NIH PROGRAM SO WELL ESTABLISHED THAT IT IS OFTEN OVERLOOKED IS A MAJOR CONTRIBUTOR TO THE STRENGTH OF CLINICAL RESEARCH IN THIS COUNTRY. THIS IS THE GENERAL CLINICAL RESEARCH CENTERS PROGRAM OF THE DIVISION OF RESEARCH RESOURCES, ESTABLISHED IN 1959 THROUGH ACTION OF THE SENATE APPROPRIATIONS COMMITTEE WHICH EXPRESSED THE BELIEF THAT NATIONAL CLINICAL RESEARCH RESOURCES WERE INADEQUATE. TODAY MORE THAN 3,000 PROJECTS ARE CONDUCTED IN THE CENTERS EACH YEAR BY AN EVEN GREATER NUMBER OF INVESTIGATORS, MOST OF WHOM ARE SUPPORTED THROUGH VARIOUS TYPES OF NIH AWARDS.

I SHOULD ALSO MENTION THE IMPORTANCE OF MAINTAINING A LEVEL OF CLINICAL TRIALS IN THIS COUNTRY IN THE FACE OF RISING COSTS OF SUCH UNDERTAKINGS. THIS IS AN AREA OF CLINICAL INVESTIGATION WHICH MUST BE MET WITH NEW AND CREATIVE MANAGEMENT. A PROGRAM RECENTLY INAUGURATED BY THE NATIONAL CANCER INSTITUTE, CALLED THE COMMUNITY CLINICAL ONCOLOGY PROGRAM, IS AN EXAMPLE OF INNOVATION ACCOMPLISHED THROUGH THE COOPERATIVE EFFORT OF THE NIH AND THE SCIENTIFIC AND MEDICAL COMMUNITY. THE PROGRAM IN 59 LOCATIONS AROUND THE COUNTRY INVOLVES COMMUNITY PHYSICIANS AFFILIATING WITH MAJOR MEDICAL CENTERS TO PARTICIPATE IN CANCER CLINICAL TRIALS. BY INCREASING SUBSTANTIALLY THE NUMBER OF PATIENTS IN TREATMENT STUDIES, THE PROGRAM WILL REDUCE THE TIME NEEDED TO COMPLETE CLINICAL TRIALS AND HASTEN THE TRANSFER OF NEW TECHNOLOGIES TO THE LOCAL LEVEL. THIS PROGRAM IS POSSIBLE ONLY BECAUSE OF THE GROWTH OF THE FIELD OF MEDICAL ONCOLOGY IN THIS COUNTRY, A FIELD WHICH INCREASED IN LARGE MEASURE DUE TO THE NATIONAL CANCER ACT FROM ABOUT 100 INDIVIDUALS IN 1970 TO ABOUT 3,000 BOARD CERTIFIED SPECIALISTS TODAY, AND BECAUSE THESE SPECIALISTS ENCOURAGE THEIR OWN CONTINUED INVOLVEMENT IN CLINICAL INVESTIGATION.

WHILE NIH PROGRAMS AND POLICIES WILL UNDOUBTEDLY HAVE A MAJOR IMPACT UPON THE FUTURE OF CLINICAL INVESTIGATION IN THIS COUNTRY, MAINTENANCE AND GROWTH OF THIS FIELD IS THE OBLIGATION OF ACADEMIC MEDICINE, THE MEDICAL PROFESSION AS A WHOLE, INDUSTRY, AND OTHER PARTS OF THE PRIVATE SECTOR, AS WELL AS GOVERNMENT. SOME MEDICAL SCHOOLS HAVE DEVELOPED CURRICULA WITH THE ASPIRING CLINICAL INVESTIGATOR IN MIND. PRIVATE SECTOR ENTITIES, SUCH AS THE AMERICAN CANCER SOCIETY AND THE AMERICAN HEART ASSOCIATION, HAVE ESTABLISHED SPECIAL AWARDS FOR PHYSICIAN-SCIENTISTS. ALL OF THESE EFFORTS CONTINUE TO MITIGATE THE CIRCUMSTANCES WHICH SEEM TO BE HINDERING THE GROWTH OF CLINICAL INVESTIGATION.

IN ADDITION, THE CURRENT GENERATION OF CLINICAL INVESTIGATORS HAS A SPECIAL RESPONSIBILITY TO PORTRAY THE SATISFACTIONS THAT CAN COME FROM CLINICAL RESEARCH

AS A CAREER. WE NEED TO LET STUDENTS KNOW THAT IN CLINICAL RESEARCH THERE IS OPPORTUNITY TO BE A CAPABLE AND CARING CLINICIAN AND ALSO TO SHARE IN THE EXCITEMENT THAT COMES FROM DISCOVERY.

BEYOND THE PERSONAL GRATIFICATION THAT COMES FROM CREATIVE WORK, CLINICAL RESEARCH OFFERS THE CHANCE TO CONTRIBUTE BOTH TO THE HEALTH OF INDIVIDUAL PATIENTS AND OF GROUPS OF PEOPLE. WE MUST KEEP STRESSING THAT, FOR THOSE EXCEPTIONAL STUDENTS WHO WILL TAKE ON THE CHALLENGE OF RESEARCH, THE REWARDS ARE GREAT.

LET ME MENTION ANOTHER MATTER WHICH IS OF DIRECT CONCERN TO THE NIH AND IS OF MORE THAN PASSING INTEREST TO THE ENTIRE RESEARCH COMMUNITY.

WITH GROWING PUBLIC AWARENESS OF THE POTENTIAL FOR SUCCESSFUL INTERVENTION IN DISEASE PROCESSES, WE CAN EXPECT CONTINUED PRESSURE FOR ADDITIONAL NARROWLY FOCUSED RESEARCH EFFORTS. IN RECENT YEARS, FOR EXAMPLE, THERE HAVE BEEN TEN PROPOSALS FOR NEW INSTITUTES AND FIVE TRANSFERS FOR MAJOR ORGANIZATIONAL STRUCTURES. SEVERAL ADDITIONAL PROPOSALS ARE PENDING BEFORE THE PRESENT CONGRESS.

IN MY OPINION, ADDITIONAL CATEGORICAL DISEASE-SPECIFIC INSTITUTES AT THE NIH WOULD NOT CONTRIBUTE TO THE MOST EFFECTIVE ADMINISTRATION OF RESEARCH AND WOULD ONLY LEAD TO FRAGMENTATION AND INCREASED ADMINISTRATIVE COSTS AT THE EXPENSE OF FUNDING FOR RESEARCH.

I AM MINDFUL OF THE HISTORY OF THE DEVELOPMENT OF THE FEDERAL BIOMEDICAL RESEARCH ENTERPRISE AND AWARE THAT THE IMPETUS FOR ITS RAPID GROWTH OFTEN CAME FROM JUST SUCH NARROW PRESSURES AS WE ARE CURRENTLY EXPERIENCING. THE NAMES OF THE CONSTITUENT INSTITUTES OF THE NIH STAND AS STATEMENTS OF THE POWER OF PUBLIC CONCERN ABOUT SPECIFIC DISEASES AND FAMILIES OF DISORDERS.

BUT THE NATURE OF RESEARCH HAS CHANGED. THERE HAS BEEN AN ACCELERATING TREND TOWARD MERGING OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SCIENCE SUBJECTS INTO A SINGLE UNIFIED DISCIPLINE. ANATOMY, PHYSIOLOGY, BIOCHEMISTRY, MICROBIOLOGY, IMMUNOLOGY, AND GENETICS ARE NOW EXPRESSED IN A COMMON LANGUAGE OF CHEMISTRY. SINCE BIOMEDICAL SCIENCE FOCUSES INCREASINGLY ON FUNDAMENTAL PROCESSES OF LIFE AND INTERRELATIONSHIPS AMONG DISEASE ENTITIES, CREATION OF ADDITIONAL CATEGORICAL DISEASE-SPECIFIC INSTITUTES IS NOT IN OUR JUDGMENT THE MOST EFFICIENT WAY TO EMPLOY NATIONAL RESOURCES FOR THE SUPPORT OF RESEARCH.

BUT HOW CAN NIH BEST SUPPORT AND MANAGE THE CONTINUING EVOLUTION OF THE HEALTH SCIENCES FOR MAXIMUM PUBLIC BENEFIT?

TO HELP RESOLVE QUESTIONS OF NIH ORGANIZATION, WE HAVE ASKED THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES TO MAKE AN 18-MONTH STUDY OF THE PRESENT STRUCTURE, TO EXAMINE ITS ADEQUACY AND EFFICIENCY, AND TO DEVISE CRITERIA BY WHICH WE CAN EVALUATE AND DETERMINE NEED FOR FUTURE CHANGE.

SEVERAL ISSUES OF CONCERN TO THE NIH AND THE RESEARCH COMMUNITY ARE BEING ADDRESSED BY THE CONGRESS. THESE INCLUDE PROPOSALS TO ESTABLISH ADDITIONAL INSTITUTES, REAUTHORIZATION OF SEVERAL NIH PROGRAMS, INDIRECT COST REIMBURSEMENTS, MISCONDUCT IN SCIENCE, ETHICAL ASPECTS OF GENETIC ENGINEERING, AND COMMERCIALIZATION OF RESEARCH. LEGISLATION INVOLVING THE USE OF ANIMALS IN RESEARCH AND TESTING IS OF PARTICULAR CONCERN FOR THE PRACTICE OF SURGERY. ALL OF THESE ISSUES DESERVE THE MOST CAREFUL CONSIDERATION. EACH OF US HAS THE RESPONSIBILITY TO RESPOND IN TERMS OF THE LONG-RANGE PERSPECTIVE OF A SCIENCE WHOSE ULTIMATE OBJECTIVE IS TO IMPROVE HUMAN HEALTH.

IN CONCLUSION I WILL VENTURE A LOOK AT THE FUTURE AND IDENTIFY A FEW OF THE ISSUES THAT I BELIEVE TO BE MOST SIGNIFICANT FOR THE CONTINUED SUCCESS OF THE AMERICAN RESEARCH ENTERPRISE.

FOREMOST IS THE NEED TO ASSURE ADEQUATE LEVELS OF SUPPORT FOR RESEARCH. I MENTIONED EARLIER THAT CURRENTLY WE ARE ABLE TO AWARD ONLY ABOUT 30 TO 35 PERCENT OF THE APPROVED APPLICATIONS FOR RESEARCH SUPPORT. WE BELIEVE THE OPTIMAL LEVEL FOR PROGRESS IS 45 TO 50 PERCENT. IN THE CONTEXT OF THE FEDERAL BUDGET, THE SUMS NEEDED ARE NOT LARGE. TO ACHIEVE SUCH A GOAL, WE WOULD NEED AN ADDITIONAL $300 TO $400 MILLION PER YEAR FOR THREE YEARS, AND THEREAFTER AN ANNUAL BUDGET OF ABOUT FIVE BILLION ADJUSTED FOR INFLATION.

ANOTHER PROBLEM IS THE NEED TO REPLACE OR PURCHASE INCREASINGLY SOPHISTICATED RESEARCH INSTRUMENTS. IT IS ESTIMATED THAT $20 MILLION A YEAR FOR FIVE YEARS IS NEEDED FOR THE ACQUISITION OF LARGE-SCALE SHARED INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE THROUGH RESEARCH GRANTS OF SMALLER INSTRUMENTS.

FINALLY, EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND MORE RECENTLY BY THE NATIONAL EYE INSTITUTE, NIH HAS LACKED AUTHORITY TO CONSTRUCT FACILITIES SINCE 1969. WE NEED TO HELP MODERNIZE AND TO CONSTRUCT NEW LABORATORIES.

I WANT TO EMPHASIZE THAT IT IS NOT POSSIBLE TO ACCOMPLISH THESE GOALS IMMEDIATELY. GIVEN THE STATE OF THE ECONOMY, NIH HAS FARED WELL. OUR BUDGET REPRESENTS A STRONG COMMITMENT BY THE ADMINISTRATION AND THE CONGRESS TO BIOMEDICAL RESEARCH, BUT I BELIEVE THAT AS THE ECONOMY IMPROVES, IT IS IMPERATIVE TO INCREASE THE LEVEL OF SUPPORT.

SOME YEARS AGO, CLARK KERR, IN HIS BOOK ON "THE USES OF THE UNIVERSITY," COMMENTED THAT "TWO GREAT IMPACTS BEYOND ALL OTHER FORCES HAVE MOLDED THE MODERN AMERICAN UNIVERSITY SYSTEM AND MADE IT DISTINCTIVE. BOTH IMPACTS HAVE COME FROM SOURCES OUTSIDE THE UNIVERSITY. BOTH HAVE COME FROM THE FEDERAL GOVERNMENT. BOTH HAVE COME IN RESPONSE TO NATIONAL NEED. THE FIRST WAS THE LAND GRANT MOVEMENT. THE SECOND GREAT IMPACT ON THE UNIVERSITIES BEGAN WITH FEDERAL SUPPORT OF SCIENTIFIC RESEARCH DURING WORLD WAR II."[4]

IN THE FIELD OF BIOMEDICAL RESEARCH, THE IMPACT OF THE SECOND EVENT HAS EXTENDED FAR BEYOND THE UNIVERSITY AND THE BENEFITS OF THE FEDERAL-ACADEMIC PARTNERSHIP HAVE PROVIDED THE MEANS FOR IMPROVEMENT OF THE QUALITY OF LIFE FOR PEOPLE THROUGHOUT THE WORLD.

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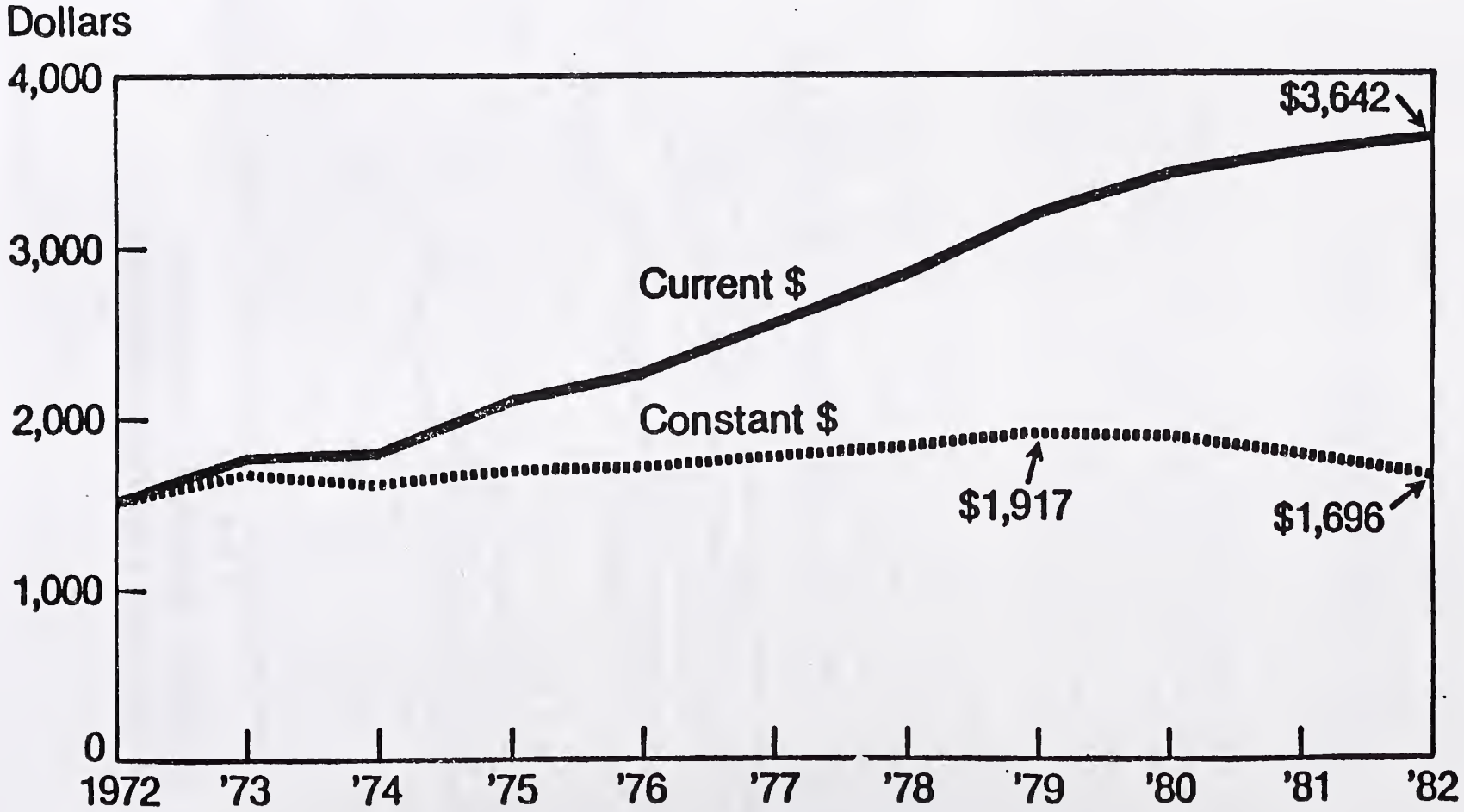
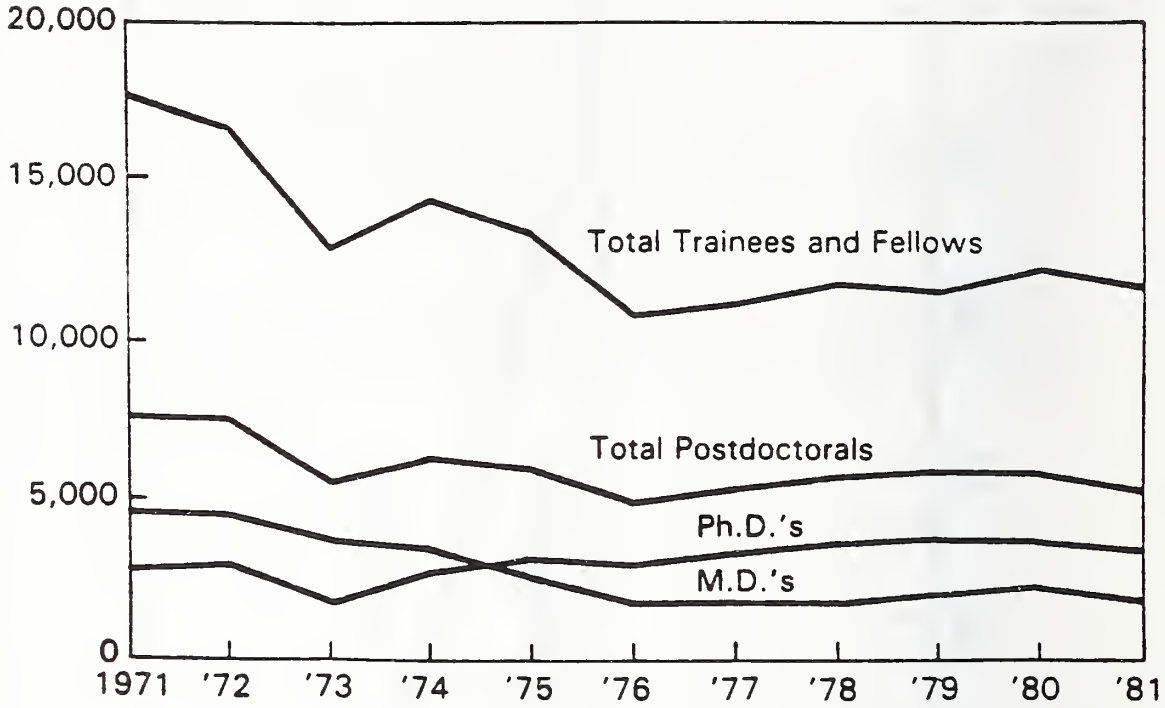
Total NIH Appropriations, 1972-82

In Current and Constant Dollars (Millions)



TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81



THE ROLE OF THE GENERAL CLINICAL RESEARCH CENTERS IN CLINICAL RESEARCH*

BY

JAMES B. WYNGAARDEN, M.D.**

I AM VERY HAPPY TO BE BACK HERE TODAY TO DELIVER THE ALEXANDER B. GUTMAN LECTURE IN CELEBRATION OF THE 20TH ANNIVERSARY OF THE MT. SINAI GENERAL CLINICAL RESEARCH CENTER (GCRC). TEN YEARS AGO I DELIVERED THE FIRST GUTMAN LECTURE ON THE PATHOGENESIS OF HYPERUREMIA AND GOUT--A RESEARCH INTEREST THAT DR. GUTMAN AND I SHARED. DR. GUTMAN WAS A GIANT, A MAN OF INTERNATIONAL STATURE. HE WAS A DISTINGUISHED SCIENTIST-CLINICIAN; A PREDIGIOUS EDITOR OF THE AMERICAN JOURNAL OF MEDICINE; A UNIVERSALLY PRODUCTIVE CLINICAL INVESTIGATOR WHOSE WORK WITH DR. YU EMBRACED EVERY IMPORTANT DEVELOPMENT IN PATHOLOGY AND DIAGNOSIS OF GOUT FOR MORE THAN TWO DECADES. WHILE MY OWN WORK ON GOUT WAS PRIMARILY FOCUSED ON DESCRIBING PURINE METABOLISM IN THE DISEASE THROUGH STUDY OF A SMALL NUMBER OF PATIENTS, DR. GUTMAN AND HIS COLLEAGUE DR. YU MADE MAJOR CONTRIBUTIONS THROUGH THE STUDY OF LARGE NUMBERS OF PATIENTS OVER TIME. PRIOR TO THEIR WORK, IT HAD BEEN REPORTED IN TEXTBOOKS OF MEDICINE AND TAUGHT IN MEDICAL SCHOOLS THAT 50 PERCENT OF GOUT PATIENTS DIED OF GOUTY RENAL FAILURE. GUTMAN AND YU'S STUDIES SHOWED, RATHER, THAT ONLY 22-25 PERCENT DIED OF RENAL FAILURE AND, MOREOVER, THAT THE RENAL FAILURE WAS OF VARYING ETIOLOGY. EVENTUALLY, GUTMAN AND YU WERE ABLE TO WHITTLE DOWN THIS PERCENTAGE EVEN FURTHER WITH THE DISCOVERY THAT SOME PATIENTS HAD GLOMERULAR NEPHRITIS. THEIRS WAS LANDMARK WORK, WHICH NOT ONLY CONTRIBUTED TO IMPROVED MANAGEMENT OF PATIENTS, BUT ALSO OPENED UP OTHER AREAS OF SCIENTIFIC INQUIRY. I AM TOLD THAT DR. GUTMAN AND DR. YU WERE HEAVY USERS OF THE GCRC WHILE THEY CONDUCTED THESE STUDIES.

TODAY, ON THIS ANNIVERSARY OF THE GCRC, IT IS FITTING THAT WE HONOR DR. GUTMAN ALSO FOR THE LEGACY HE LEFT HERE AS CO-FOUNDER OF THE GCRC. IT IS INTERESTING THAT DRS. GUTMAN AND KUPFER WERE ABLE TO BEGIN THE GCRC IN 1963, THE SAME YEAR THAT THE SCHOOL OF MEDICINE WAS GRANTED A PROVISIONAL CHARTER BY THE BOARD OF REGENTS OF THE UNIVERSITY OF THE STATE OF NEW YORK, AND ABOUT THREE YEARS BEFORE THE MEDICAL SCHOOL WAS OFFICIALLY OPENED.

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Mt. Sinai School of Medicine, New York
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**Director, National Institutes of Health

AT THE TIME I GAVE THE FIRST GUTMAN LECTURE I WAS HEAD OF THE DEPARTMENT OF MEDICINE AT DUKE. BECAUSE OF MY EXPERIENCES WITH THE DUKE GCRC, I UNDERSTOOD THE EXCITEMENT THAT CAN BE GENERATED IN SUCH A CLINICAL RESEARCH SETTING. BUT IT WAS NOT UNTIL I CAME TO NIH AS DIRECTOR AND LEARNED MORE ABOUT ITS HISTORY AND ITS GUIDING PRINCIPLES THAT I BEGAN TO APPRECIATE MORE FULLY THAT THE GCRC IS A NATIONAL RESOURCE, A MICROCOSM OF THE FEDERAL GOVERNMENT-MEDICAL SCHOOL PARTNER- SHIP.

I HOPE IN MY TALK TO PROVIDE A PICTURE OF THE WHOLE GCRC PROGRAM AND HOW IT FITS INTO THE MOSAIC OF NIH SUPPORT MECHANISMS. I ALSO WANT TO DISCUSS THE CURRENT STATUS OF CLINICAL INVESTIGATION AND TO PROVIDE SOME SUGGESTIONS ABOUT WHAT OUR PARTNERSHIP CAN CONTRIBUTE--THROUGH GCRC'S AND OTHER MEANS--TO HELP NURTURE THE CLINICAL INVESTIGATOR AND GUARANTEE THAT THE ENTERPRISE WILL CONTINUE TO FLOURISH.

ALTHOUGH NIH WILL OBSERVE ITS CENTENNIAL IN A FEW YEARS, FOR MORE THAN HALF OF ITS HISTORY, THE AGENCY HAD LITTLE OR NO CONTACT WITH ACADEMIC INSTITUTIONS. FROM THE PERSPECTIVE OF BIOMEDICAL RESEARCH, THE ACTIVE PARTNERSHIP OF THE FEDERAL GOVERNMENT AND ACADEMIC SCIENCE BEGAN UNDER THE PRESSURES OF WORLD WAR II, WHEN, IN ORDER TO INITIATE AND SUPPORT SCIENTIFIC RESEARCH ON MEDICAL PROBLEMS AFFECTING THE NATIONAL DEFENSE, THE GOVERNMENT TURNED TO THE ACADEMIC SECTOR. IN 1941, ONLY SIX OF THE 71 FOUR-YEAR AMERICAN MEDICAL SCHOOLS REPORTED ANY INCOME FROM THE FEDERAL GOVERNMENT. THE GRAND TOTAL OF SUCH SUPPORT WAS LESS THAN $200,000! TODAY, 52 PERCENT OF NIH'S BUDGET, OR $1.521 BILLION, IS DISPERSED TO MEDICAL SCHOOLS. SLIDE 1.

THE MASTERMIND BEHIND THE FORMATION OF THE PARTNERSHIP WAS VANNEVAR BUSH, THE PRESIDENT'S SCIENCE ADVISOR, WHO IN 1945 WROTE A REPORT TITLED: "SCIENCE--THE ENDLESS FRONTIER." IN IT HE LAID OUT THE PHILOSOPHICAL GROUNDING FOR THE PARTNERSHIP. HE WROTE: "THE PUBLICLY AND PRIVATELY-SUPPORTED COLLEGES, UNIVERSITIES, AND RESEARCH INSTITUTES ARE THE CENTERS OF BASIC RESEARCH. THEY ARE THE WELLSPRINGS OF KNOWLEDGE AND UNDERSTANDING. AS LONG AS THEY ARE VIGOROUS AND HEALTHY AND THEIR SCIENTISTS ARE FREE TO PURSUE THE TRUTH WHEREVER IT MAY LEAD, THERE WILL BE A FLOW OF NEW SCIENTIFIC KNOWLEDGE...."

THUS, BUSH IDENTIFIED THE ACADEMIC INSTITUTIONS AS THE APPROPRIATE ENVIRONMENT FOR RESEARCH AND ADVISED AGAINST RELIANCE ON THE FREE-STANDING RESEARCH INSTITUTE AS THE DOMINANT MECHANISM FOR MEETING THE NATION'S NEEDS.

THE BEDROCK MECHANISM OF SUPPORT IN THIS NIH-MEDICAL SCHOOL PARTNERSHIP HAS BEEN AND WILL CONTINUE TO BE THE RESEARCH PROJECT GRANT TO INDIVIDUAL INVESTIGATORS, REVIEWED FOR MERIT BY SCIENTIFIC PEERS. NIH STILL HOLDS TO THE PRINCIPLE THAT HIS TYPE OF RESEARCH IS MOST LIKELY TO PRODUCE INNOVATIVE, CREATIVE, AND BENEFICIAL RESEARCH. BUT, AS NIH EXPANDED FROM 1955 TO THE LATE 1960'S, COROLLARY OBJECTIVES ALSO EMERGED: THE STRENGTHENING OF THE INSTITUTIONS IN WHICH BIOMEDICAL RESEARCH WOULD BE DONE, AND THE DEVELOPMENT OF TRAINING MECHANISMS THAT WOULD ENSURE A CONTINUING SUPPLY OF COMPETENT SCIENTISTS DRAWN FROM THE BEST AND BRIGHTEST IN THE UNIVERSITIES.

THE TWO ELEMENTS--SUPPORT OF RESEARCH AND THE HEALTH OF THE RESEARCH INSTITUTIONS--ARE INSEPARABLY LINKED TO ONE ANOTHER. THE FEDERAL GOVERNMENT--NIH--IN CARRYING OUT ITS RESEARCH MISSION IS, IN FACT, DEPENDENT UPON THE NATION'S SCIENTIFIC COMMUNITY. OUR CONCERN IS ENHANCED TODAY AS INSTITUTIONS ARE CONTENDING WITH AN ARRAY OF TROUBLESOME ISSUES: PHILANTHROPY ON THE WANE, THE DISAPPEARANCE OF CONSTRUCTION GRANTS, AND REDUCTIONS IN REIMBURSEMENT OF PATIENT CARE AND A STEADY-STATE BUDGET AT NIH.

IN ADDITION TO PROVIDING A CONSTANT FLOW OF NEW, YOUNG TALENT, THE ACADEMIC INSTITUTION HISTORICALLY HAS AN ADDITIONAL CHARACTERISTIC WHICH MAKES IT A NATURAL ENVIRONMENT FOR RESEARCH--A TRADITION OF ACADEMIC FREEDOM WHICH PROTECTS THE ABILITY OF THE RESEARCHER TO FOLLOW LEADS AS HE OR SHE IS DRAWN.

THE ACADEMIC HEALTH CENTER HAS MUCH TO GAIN FROM ITS RESEARCH COMPONENT. THE LINKING OF RESEARCH AND TEACHING IS VALUABLE TO BOTH ENTERPRISES. EDUCATION IS DIMINISHED IF IT DOES NOT EXPOSE STUDENTS TO COMMITTED SCHOLARS AND RESEARCHERS. MOREOVER, THE RESEARCH ENTERPRISE ALSO GAINS, FOR STUDENTS WITH FRESH IDEAS OFTEN STIMULATE THEIR MENTORS IN THE EXPLORATION OF NEW AVENUES. THE HEALTH CARE COMPONENT OF THE ACADEMIC CENTER AND THE RESEARCH UNDERTAKING ALSO PROVIDE MUTUAL ENCHANCEMENT.

THE AUDITORIUM OF THE NIH CLINICAL CENTER HAS A QUOTATION CARVED IN THE MARBLE WALL AT ITS ENTRANCE, A QUOTATION FROM ITS FIRST DIRECTOR, DR. JACK MASUR, FOR WHOM THE AUDITORIUM IS NAMED, THAT BEAUTIFULLY CAPTURES THIS CONCEPT. IT READS: "HOSPITALS WITH LONG TRADITIONS OF EXCELLENCE HAVE DEMONSTRATED ABUNDANTLY THAT RESEARCH ENHANCES THE VITALITY OF TEACHING; TEACHING LIFTS THE STANDARDS OF SERVICE; AND SERVICE OPENS NEW AVENUES OF INVESTIGATION."

SO THE GCRC'S—WHICH ARE FULLY GROUNDED IN THE HISTORY AND PHILOSOPHY OF THE NIH--INDIVIDUALLY ARE MICROCOSMS OF THE NIH-MEDICAL SCHOOL PARTNERSHIP. EACH INCLUDES INVESTIGATORS SUPPORTED THROUGH NIH PROJECT GRANTS, WITH CORE SUPPORT, AND WITH A STRONG TRAINING ELEMENT AS WELL. THEY REPRESENT NIH'S COMMITMENT TO INVESTIGATOR-INITIATED RESEARCH, TO THE STABILITY OF THE RESEARCH ENVIRONMENT, AND TO THE FUTURE OF THE RESEARCH ENTERPRISE THROUGH TRAINING.

THE GCRC PROGRAM AT THE NIH HAD ITS ORIGINS IN 1959 WHEN THE U.S. SENATE APPROPRIATIONS COMMITTEE, PERCEIVING THE NEED TO INCREASE PATIENT-ORIENTED RESEARCH, URGED THAT CLINICAL RESEARCH CENTERS BE ESTABLISHED THROUGHOUT THE COUNTRY TO IMPROVE AND INTENSIFY THE SCIENTIFIC ATTACK ON MAN'S DISEASES AND THEIR BASIC BIOLOGIC PARAMETERS. A $3 MILLION APPROPRIATION CREATED EIGHT CENTERS IN 1960, AND BY 1962, WHEN THE DIVISION OF RESEARCH FACILITIES AND RESOURCES ASSUMED RESPONSIBILITY FOR THE PROGRAM, IT HAD GROWN TO 60 CENTERS. BY 1966, 93 CENTERS HAD BEEN ESTABLISHED.

SUBSEQUENT TO THIS PERIOD OF GROWTH, A NUMBER OF NEEDS AND OPPORTUNITIES AROSE FOR IMPROVING AND ENHANCING OPERATIONS. CHANGES INCLUDED IMPLEMENTATION OF A SERVICE PATIENT POLICY TO ALLOW FOR THIRD PARTY PAYMENT FOR SOME PATIENTS AND TO MAKE USE OF BEDS MORE COST EFFECTIVE. IN 1970, PROVISION WAS MADE FOR OUTPATIENT RESEARCH FACILITIES WITHIN THE EXISTING CENTERS. SLIDE 2 SHOWS THE CONTINUED INCREASE IN OUTPATIENT VISITS FROM 1,200 OUTPATIENT VISITS IN 1970 TO MORE THAN 100,000 IN 1981. THIS OUTPATIENT RESEARCH ELEMENT OF THE PROGRAM HAS BEEN VERY PRODUCTIVE, HAVING CONTRIBUTED TO 1200 PUBLICATIONS AND 721 ABSTRACTS IN 1977 ALONE! THESE CHANGES IN APPROACH, AS WELL AS INTENSIFIED APPLICATION OF THE PRINCIPLES OF RIGID PEER REVIEW, HAVE RESULTED IN A PROGRAM SUBSTANTIALLY DIFFERENT AND IMPROVED FROM ITS COUNTERPART OF A LITTLE MORE THAN A DECADE AGO. SLIDE 3.

IN 1970 THERE WERE 93 CENTERS WITH 904 BEDS, FUNDED AT A LEVEL OF ABOUT $35 MILLION. THE NUMBER OF CENTERS DROPPED GRADUALLY TO 74 IN 1982 (NOW 75) WITH 595 BEDS FUNDED AT A LEVEL OF ABOUT $64 MILLION. TAKEN TOGETHER, THE GCRC NETWORK--IN TERMS OF NUMBER OF PATIENT BEDS--IS THE EQUIVALENT OF THE INPATIENT ACTIVITY OF THE NIH CLINICAL CENTER.

THE BUDGET HISTORY OF THE GCRC'S PROGRAM INDICATES THAT FUNDING LEVELS IN CONSTANT DOLLARS HAVE DECREASED OVER THE YEARS, THEN LEVELED, AS IS TRUE OF THE NIH BUDGET AS A WHOLE AND OF MANY OTHER ELEMENTS IN THE BUDGET. SLIDE 4.

AS FOR THE CONTENT OF THE PROGRAM, IT SUPPORTS 80 PERCENT OF THE RESEARCH INPATIENT CARE FOR THE EXTRAMURAL PROGRAM OF THE NIH CATEGORICAL INSTITUTES. SLIDE 5. MORE THAN 3,300 PROJECTS ARE CONDUCTED AT THE CENTERS EACH YEAR BY AN EVEN GREATER NUMBER OF INVESTIGATORS, MOST OF WHOM RECEIVE SUPPORT FROM RESEARCH GRANTS, TRAINING GRANTS, PROGRAM PROJECT GRANTS, NIH CONTRACTS, OR CAREER DEVELOPMENT AWARDS.

THE NIH COMPONENTS MOST INTERACTIVE WITH THE GCRC'S ARE, IN THIS ORDER, THE NIADDK, THE NHLBI, THE NCI AND THE NICHD. ANOTHER WAY OF LOOKING AT PROGRAM CONTENT IS BY BROAD DISCIPLINARY CATEGORIES (TRANS-NIH ACTIVITIES). SLIDE 6 SHOWS SOME OF THOSE CATEGORIES: IN 1982, THE CENTERS REPORTED PROJECTS COSTING MORE NEARLY $2.3 MILLION IN ARTHRITIS, ALMOST $13 MILLION IN DIABETES; ABOUT $10 MILLION IN DIGESTIVE DISEASES; AND ABOUT $11.5 MILLION IN NUTRITION. THIS SLIDE GIVES SOME IDEA OF PROGRAM SUPPORT IN A FEW RESEARCH AREAS OF PARTICULAR PUBLIC INTEREST. MEASURES OF PROGRAM QUALITY ARE SOMEWHAT MORE DIFFICULT TO MAKE, BUT IN TERMS OF PUBLICATIONS, THE PROGRAM HAS HAD A MORE THAN 50 PERCENT INCREASE IN OUTPUT SINCE 1970. MOREOVER, THERE HAS BEEN A STEADY INCREASE IN PUBLICATIONS RESULTING FROM OUTPATIENT STUDIES. THUS, THE PROGRAM SEEMS TO BE FAR MORE PRODUCTIVE THAN IT WAS TEN YEARS AGO DESPITE THE SUBSTANTIAL DECREASE IN THE NUMBER AND SIZE OF CENTERS SUPPORTED.

SEVERAL OTHER FEATURES OF THE GCRC'S MERIT ATTENTION: A PROTOTYPE COMPUTER-BASED DATA MANAGEMENT SYSTEM WAS TESTED BY CLINICAL INVESTIGATORS IN 1977 AND FOUND TO BE SO USEFUL THAT THE SO-CALLED "CLINFO" HAS BEEN AWARDED TO 22 CENTERS, WITH MORE EXPECTED TO BE INSTALLED IN THE FUTURE.

THE FUTURE OF CLINICAL INVESTIGATION DEPENDS UPON AN ADEQUATE SUPPLY OF WELL-TRAINED INVESTIGATORS DEDICATED TO CLINICAL RESEARCH. RECOGNIZING THIS, THE GCRC PROGRAM IN 1974 INITIATED THE CLINICAL ASSOCIATE PHYSICIAN (CAP) PROGRAM. THIS PROGRAM, DESIGNED TO ENCOURAGE YOUNG PHYSICIANS TO ENTER CAREERS IN CLINICAL INVESTIGATION, HAS SINCE PRODUCED 93 GRADUATES, OF WHOM APPROXIMATELY 80 PERCENT HAVE REMAINED IN ACADEMIC MEDICINE. TO DATE, HALF OF THESE GRADUATES IN ACADEMIC MEDICINE HAVE OBTAINED NIH SUPPORT FOR THEIR CLINICAL RESEARCH INVESTIGATIONS.

IN ADDITION, THE GCRC PROGRAM HAS FOR THE PAST FIVE YEARS HAD A VERY POPULAR MEDICAL STUDENT PROGRAM WHICH PROVIDES EXPOSURE TO CLINICAL RESEARCH FOR PERIODS OF 3-6 MONTHS.

THE GCRC'S REALLY CONSTITUTE A UNIQUE ENVIRONMENT, PROBABLY FOUND ELSEWHERE ONLY AT THE NIH CLINICAL CENTER AND IN THE COMPREHENSIVE CANCER CENTERS, FOR A VERY SPECIAL KIND OF RESEARCH, INDEED, A VERY SPECIAL KIND OF CLINICAL RESEARCH. BECAUSE OF ITS VERY NATURE, THE GCRC PROVIDES AN ATMOSPHERE WHERE THE MANY PATHS OF INQUIRY AND DISCOVERY ABOUT LIFE PROCESSES, PARTICULARLY THOSE WHICH STEM FROM EFFORTS TO UNDERSTAND AND INTERVENE IN STATES OF DISEASE, CAN FLOURISH. ALMOST EVERYONE CAN APPRECIATE THE CONTRIBUTIONS TO HUMAN HEALTH GAINED THROUGH THE "BENCH TO BEDSIDE CONNECTION." BUT THAT IS ONLY ONE POSSIBLE PATH TO SCIENTIFIC DISCOVERY. THE GCRC PROVIDES A MILIEU IN WHICH THE PATH OF INQUIRY CAN FLOW IN THE OPPOSITE DIRECTION--FROM "BEDSIDE TO BENCH"; PRODUCING MAJOR ADVANCES IN OUR UNDERSTANDING OF FUNDAMENTAL BIOLOGICAL PHENOMENA.

MANY HAVE EXPRESSED THEIR CONCERNS IN RECENT YEARS ABOUT THE STATE OF THIS TWO-WAY FLOW. DR. DAVID A. HAMBURG, FORMER PRESIDENT OF THE INSTITUTE OF MEDICINE, PUT IT WELL IN 1980[1]. "WE MUST DO EVERYTHING IN OUR POWER TO SEE THAT THE GREAT FUNDAMENTAL ADVANCES--INDEED THE INSPIRING ADVANCES IN MOLECULAR AND CELLULAR BIOLOGY--WILL BE AVAILABLE AS SOON AS POSSIBLE FOR HEALTH INTERVENTIONS OF A DEMONSTRABLY USEFUL CHARACTER. BUT THE AUTHENTIC BIOLOGICAL REVOLUTION THAT HAS BEEN GENERATED BY SEVERAL DECADES OF INTENSIVE BASIC RESEARCH IS NOT EASILY TRANSLATED INTO CLINICALLY VALID APPLICATIONS. AN INTERPRETER IS NEEDED, AND IT IS THE CLINICAL INVESTIGATOR WHO SERVES THAT FUNCTION. THE FLOW OF INFORMATION IS BY NO MEANS UNIDIRECTIONAL; IF BASIC SCIENCE HAS SOMETHING TO SAY TO CLINICAL INVESTIGATION, SO TOO DOES CLINICAL INVESTIGATION OFFER MUCH TO BASIC SCIENCE. CLINICAL RESEARCH REMAINS THE VITAL BRIDGE BETWEEN ADVANCES IN BASIC SCIENCE ON THE ONE HAND AND IMPROVEMENTS IN HEALTH CARE--DIAGNOSTIC, THERAPEUTIC OR PREVENTIVE—ON THE OTHER."

DR. HAMBURG WENT ON TO SAY, "I WAS CONCERNED IN 1975, AND REMAIN CONCERNED TODAY, THAT THE INTERWOVEN FABRIC OF BASIC SCIENCE AND CLINICAL INVESTIGATION IS TO SOME EXTENT UNRAVELING."

I WOULD LIKE TO EXAMINE HIS CONCERN, WHICH, TO SOME EXTENT, I SHARE. WE--NIH AND THE SCIENTIFIC COMMUNITY— NEED TO LOOK AT A NUMBER OF FACTORS THAT APPEAR TO BE CONTRIBUTING TO A DECLINING INTEREST IN CLINICAL INVESTIGATION ON THE PART OF YOUNG PHYSICIANS.

LET US LOOK AT SOME OF THE DATA SURROUNDING THIS ISSUE. SLIDE 7.

THE ABSOLUTE NUMBER OF NIH RESEARCH GRANTS (RO1'S) AWARDED TO M.D.'S FELL FROM ABOUT 3,400 IN 1968 TO ABOUT 2,500 IN 1973. THERE HAS BEEN SOME RECOVERY SINCE, BUT THE NUMBER WAS STILL BELOW 3,000 IN 1982. THE NUMBER OF GRANTS TO MD/PH.D.'S (AND THESE ARE, OF COURSE, IN MUCH SMALLER NUMBERS) IS HOLDING RATHER STEADY.

SLIDE 8. THE PERCENTAGE OF M.D.'S HOLDING NIH RESEARCH GRANTS HAS PROGRESSIVELY FALLEN OVER THE YEARS. M.D./PH.D.'S COMPRISE A RELATIVELY SMALL PROPORTION OF THE GRANT HOLDERS AND THIS GROUP HAS REMAINED RELATIVELY CONSTANT. CURRENTLY PH.D.'S HOLD APPROXIMATELY 68% OF THE NIH RESEARCH GRANT (RO1) PORTFOLIO WHILE M.D'S HOLD ONLY ABOUT 22 PERCENT. IF MD/PH.D.'S ARE ADDED, THE PERCENTAGE HELD BY THOSE WITH PROFESSIONAL DEGREES CLIMBS TO ABOUT 31%. THUS, THE PROPORTION OF RESEARCH GRANTS AWARDED TO M.D. INVESTIGATORS IS ABOUT ONE-HALF THAT OF A DECADE AGO. NIH CURRENTLY FUNDS MORE THAN 16,000 RO1 TYPE RESEARCH GRANTS, COMPARED WITH 9000 IN 1972. THE INCREMENT IN THE NUMBER OF SUCH GRANTS HAS GONE ALMOST ENTIRELY TO PH.D. APPLICANTS. MEANWHILE, MANY ADDITIONAL M.D.'S ARE PARTICIPATING IN OTHER RESEARCH MECHANISMS, SUCH AS SPECIALIZED RESEARCH CENTERS AND CLINICAL TRIALS.

THE DECLINE IN THE PERCENTAGE OF M.D. INVESTIGATORS WORKING UNDER RO1 GRANTS REFLECTS IN PART THE SUBMISSION OF FEWER GRANT APPLICATIONS BY M.D. THAN PH.D. SCIENTISTS. IN 1970, M.D.'S COMPRISED ABOUT 30 PERCENT OF THE APPLICANTS; BY 1980, ONLY 24 PERCENT. ANOTHER IMPORTANT FACTOR IS THE INTENSE COMPETITION.

SLIDE 10. WHEN ONE LOOKS AT THE SUCCESS RATE OF NEW APPLICANTS ALONE, ONE FINDS THAT THERE HAS BEEN A DIVERGENCE SINCE ABOUT 1974, WITH NEW M.D. APPLICANTS COMPETING LESS WELL THAN NEW PH.D. APPLICANTS, WITH BOTH GROUPS COMPETING LESS SUCCESSFULLY THAN THE MD/PH.D. APPLICANT.

ONE FACTOR THAT MAY BE PLAYING A ROLE IN THE RECORD FOR M.D. APPLICANTS IS THE FACT THAT APPLICATIONS FOR CLINICAL RESEARCH TEND TO FARE LESS WELL THAN BASIC SCIENCE APPLICATIONS IN THE NIH GRANT REVIEW SYSTEM.

CLINICAL RESEARCH APPLICATIONS--THOSE INVOLVING HUMAN SUBJECTS OR HUMAN TISSUES—ARE MORE OFTEN DISAPPROVED AND MORE OFTEN ASSIGNED POORER PRIORITY SCORES THAN ARE APPLICATIONS IN WHICH NO HUMAN SUBJECTS ARE INVOLVED.

AS THE NEXT SLIDE INDICATES, SLIDE 11, APPROVAL RATES FOR STUDIES WHICH DON'T INVOLVE HUMAN SUBJECTS ARE SUBSTANTIALLY HIGHER THAN THOSE FOR STUDIES WITH HUMAN SUBJECTS, REGARDLESS OF WHETHER THE PRINCIPAL INVESTIGATOR IS AN M.D. OR A PH.D.

IN ORDER TO DISCOVER WHY APPLICATIONS TO NIH FOR GRANTS TO CONDUCT CLINICAL RESEARCH MAY EITHER BE DISAPPROVED OR RECEIVE POOR PRIORITY IN THE REVIEW PROCESS, THE DIVISION OF RESEARCH GRANTS EXAMINED 256 APPLICATIONS RATED BY 13 DIFFERENT STUDY SECTIONS.[3] SLIDE 12. FOR THIS STUDY, CLINICAL RESEARCH WAS NARROWLY DEFINED AS RESEARCH INVOLVING HUMAN SUBJECTS THAT INCLUDED A DOCTOR-PATIENT RELATIONSHIP. IT IS IMPORTANT TO NOTE THAT INVESTIGATOR QUALIFICATIONS AND RESOURCES AT THEIR INSTITUTIONS PLAYED A VERY MINOR ROLE IN POOR RATING. FLAWS IN RESEARCH DESIGN AND CONCEPTION OF THE HYPOTHESIS LED TO POOR SCORES FROM REVIEWERS. THE MOST FREQUENT DEFICIENCIES-- FAULTY HYPOTHESES AND INAPPROPRIATE EXPERIMENTAL DESIGN--WERE THE SAME FLAWS THAT WERE CITED IN THE BASIC RESEARCH PROPOSALS THAT ARE DISAPPROVED.

THE FACILE EXPLANATION OF THE GREATER DIFFICULTY INHERENT IN WORKING WITH HUMAN SUBJECTS MAY NOT BE THE ENTIRE ANSWER TO THE LOWER APPROVAL RATES FOR PHYSICIAN-INVESTIGATORS. SCIENCE HAS BECOME COMPLEX, THE METHODS INTRICATE AND THE TRAINING PERIOD SO LONG THAT THE PHYSICIAN, EVEN AFTER TWO OR THREE YEARS OF FELLOWSHIP TRAINING, REMAINS LESS WELL-TRAINED THAN THE PH.D. SCIENTIST WHO HAS BEEN TRAINING FOR A RESEARCH CAREER SINCE THE BACCALAUREATE. IN MY VIEW, THE TRENDS OF THE PAST DECADE REFLECT THE PROGRESSIVE PROFESSIONALIZATION OF BIOMEDICAL RESEARCH, IN PARTICULAR OF CLINICAL RESEARCH. I HOPE THERE WILL ALWAYS BE ROOM FOR THE CREATIVE AMATEUR IN CLINICAL INVESTIGATION, BUT RECENT HISTORY INDICATES THAT SUCH A PERSON IS LESS AND LESS LIKELY TO SECURE EXTERNAL SUPPORT FOR HIS OR HER WORK. SUCCESS FOR AN M.D. INVESTIGATOR IS INCREASINGLY DEPENDENT UPON SUBSTANTIAL TRAINING IN THE INFORMATION, CONCEPTS, AND METHODOLOGIES OF COMPLEX MODERN SCIENCE. TO BE A FIRST- RATE SCIENTIST AND A WELL-QUALIFIED PHYSICIAN IS A DEMANDING CALLING.

THE INTEGRAL RELATIONSHIP BETWEEN TRAINING AND LATER CONDUCT OF RESEARCH SEEMS ALMOST SELF-EVIDENT. ONE STUDY BY THE AAMC[4] HAS SHOWN THAT FOR BOTH M.D.'S AND PH.D.'S, POSTDOCTORAL TRAINING HAS THE GREATEST INFLUENCE ON APPROVAL RATE ON FIRST RESEARCH GRANT APPLICATIONS, WITH OTHER SIGNIFICANT FACTORS BEING THE INSTITUTION CONFERRING THE DEGREE AND THE PLACE OF EMPLOYMENT.

BECAUSE OF THE ESTABLISHED PRIMACY OF POSTDOCTORAL TRAINING IN ENHANCING THE PARTICIPATION OF PHYSICIAN INVESTIGATORS IN INDEPENDENT RESEARCH, IT IS IMPORTANT TO LOOK AT THE STATUS OF NIH TRAINING LEVELS IN ORDER TO ASSESS ACCURATELY THE FUTURE PICTURE FOR CLINICAL RESEARCH.

THE NUMBERS OF M.D. TRAINEES AND FELLOWS FELL FROM ABOUT 4,600 TO ABOUT 1,900 BETWEEN FY 1971 AND 1981. THIS SEEMINGLY DRASTIC DECLINE IS SOMEWHAT ARTIFICIAL BECAUSE CESSATION OF FEDERAL SUPPORT FOR CLINICAL TRAINING IN THE EARLY 1970'S CONTRIBUTED TO THE DROP-OFF.

SLIDE 14. DATA FROM 1975 TO THE PRESENT CORRESPOND TO THE INCEPTION AND DEVELOPMENT OF THE NATIONAL RESEARCH SERVICE AWARD (NRSA) PROGRAM. WE SEE THE DECLINE IN M.D. PARTICIPATION CONTINUING TO FY 1976 AND THEN APPARENTLY LEVELING OFF. AT THE SAME TIME, PH.D. PARTICIPATION HAS INCREASED.

THE MODIFICATION IN AUTHORITY IN 1974, UNDER THE NATIONAL RESEARCH SERVICE AWARDS ACT, LIMITS TRAINING EXCLUSIVELY TO RESEARCH OR ACADEMIC DEVELOPMENT. UNDER THE SAME ACT, A COMMITTEE OF THE NATIONAL ACADEMY OF SCIENCES HAS RECOMMENDED THAT 2,800 CLINICAL RESEARCH TRAINING SLOTS BE OFFERED BY NIH ANNUALLY--2,400 AS TRAINEESHIPS, AND 400 AS DIRECT FELLOWSHIPS. THIS FIGURE OF 2,800 CLINICAL TRAINING POSITIONS WAS NOT REACHED UNTIL 1980, BUT AT THAT TIME 900 OF THESE CLINICAL TRAINEESHIPS WERE HELD BY PH.D. TRAINEES, (TWICE THE NUMBER ONLY THREE YEARS AGO) AND ONLY 1,900 BY M.D. TRAINEES. THE ACADEMY COMMITTEE HAS RECOMMENDED THAT AT LEAST 85 PERCENT OF THE TRAINEESHIPS IN THIS CATEGORY OR ABOUT 2,400 BE FILLED BY M.D.'S. SO, BY EVERY YARDSTICK, WE ARE FAILING TO ATTRACT THE NUMBER OF QUALIFIED PHYSICIANS INTO RESEARCH TRAINING PERCEIVED TO BE DESIRABLE BY THE ACADEMY COMMITTEE. FORTUNATELY, SOME OF THIS GAP IS BEING FILLED BY PH.D. SCIENTISTS INTERESTED IN CLINICAL RESEARCH. BUT THIS SHORTFALL OF PHYSICIAN INVESTIGATORS ALTERS THE BALANCE BETWEEN M.D. AND PH.D. INVESTIGATORS DEEMED ESSENTIAL FOR COORDINATED PROGRESS IN BASIC SCIENCE AND CLINICAL RESEARCH.

MANY REASONS HAVE BEEN CITED FOR THE DECLINING INTEREST OF PHYSICIANS IN CLINICAL RESEARCH. MOST MEDICAL SCHOOL CURRICULA PROVIDE LITTLE OR NO LABORATORY EXPERIENCE THAT IS REPRESENTATIVE OF MODERN DAY MEDICAL SCIENCE. THE RISE OF SPECIALTY FIELDS AND THE LENGTHENING OF POSTDOCTORAL TRAINING PROGRAMS HAVE EXTENDED THE CLINICAL TRAINING NECESSARY FOR BOARD CERTIFICATION. THE REQUIREMENTS OF MANY CERTIFICATION BOARDS ARE RATHER INFLEXIBLE AND CERTAINLY DO NOT ENCOURAGE THE POTENTIALLY CREATIVE PHYSICIAN TO ENTER RESEARCH TRAINING.

OTHER CONSIDERATIONS MAY ACT AS DETERRENTS FOR SOME POTENTIAL TRAINEESHIP APPLICANTS. PERHAPS DOMINATING THE ISSUES IS THAT OF THE FINANCIAL DISINCENTIVES, BOTH BETWEEN THE THIRD-YEAR RESIDENCY SALARY AND THE FIRST-YEAR TRAINEESHIP, WHICH NOW EXHIBITS AN AVERAGE GAP OF $6,000, AND THE SUBSTANTIALLY LARGER DIFFERENCES BETWEEN THE INCOME POSSIBILITIES IN RESEARCH AND IN PROCEDURE-ORIENTED PRACTICES OF MEDICINE. AND ESPECIALLY WHEN THE DEBT LOAD INCURRED BY THE GRADUATING STUDENT IS $20,000 OR MORE, THE CUMULATIVE FINANCIAL DISINCENTIVES ARE A MAJOR FACTOR IN DISSUADING POTENTIAL INVESTIGATORS FROM ENTERING THE FIELD.

NIH HAS DEVOTED CONSIDERABLE ATTENTION TO THIS PROBLEM AND HAS INTRODUCED SOME MAJOR STEPS TOWARD ITS SOLUTION.

AT THE UNDERGRADUATE MEDICAL STUDENT LEVEL, WE HAVE CONTINUED TO GIVE THE MEDICAL SCIENTIST TRAINING PROGRAM (MSTP) TOP PRIORITY IN OUR TRAINING PORTFOLIO.

IN THE MSTP THIS YEAR, WE WILL SUPPORT ABOUT 650 STUDENTS MOVING TOWARD A COMBINED M.D./PH.D. DEGREE. WE REGARD THIS PROGRAM AS ONE OF OUR MOST SUCCESSFUL IN TERMS OF BUILDING UP CLINICAL RESEARCH. THIS SIX-YEAR PROGRAM MAKES AWARDS TO 24 SCHOOLS. SEVENTY PERCENT OF THE GRADUATES HOLD POSITIONS IN ACADEMIC MEDICINE DOING RESEARCH AND ENGAGING IN THE TRAINING OF OTHER PHYSICIANS. THE PROGRAM WILL BE STRENGTHENED TO SUPPORT APPROXIMATELY 700 STUDENTS PER YEAR, RESULTING IN PRODUCTION OF MORE THAN 100 GRADUATES PER YEAR OF THE TYPE OF SCIENTIST CURRENTLY COMPETING MOST SUCCESSFULLY FOR R01 RESEARCH SUPPORT.

THE NIH ALSO HAS A NUMBER OF PROGRAMS THAT PROVIDE EARLY STUDENT EXPOSURE TO RESEARCH CAREERS. THIS PAST YEAR MORE THAN 1,100 MEDICAL STUDENTS AVAILED THEMSELVES OF OFF-QUARTER TRAINING OPPORTUNITIES SUPPORTED BY NIH. WITH THE NEW EXEMPTION OF THE FIRST YEAR OF NRSA SUPPORT FROM PAYBACK OBLIGATION, THE NIH LAST YEAR REINSTITUTED THE POST- SOPHOMORE FELLOWSHIP OR ITS EQUIVALENT, TO PROVIDE A FULL YEAR OF RESEARCH TRAINING WITHIN THE MEDICAL SCHOOL EXPERIENCE UNDER AN NIH FELLOWSHIP OR TRAINEESHIP. THE NIH ALSO OFFERS SUMMER RESEARCH FELLOWSHIPS AT BETHESDA, AND DURING THIS PAST YEAR 52 MEDICAL STUDENTS PARTICIPATED IN THAT PROGRAM.

THE PHYSICIAN WHO HAS COMPLETED FOUR YEARS OF MEDICAL SCHOOL AND SEVERAL YEARS OF CLINICAL TRAINING IS, BY AND LARGE, ONLY MODESTLY PREPARED WITH RESEARCH SKILLS. EVEN WHERE SUCCESSFUL PARTICIPATION IN ONE OR MORE RESEARCH PROJECTS HAS TAKEN PLACE, THE EXPERIENCE DOES NOT SUBSTITUTE FOR A PLANNED PROGRAM TO DEVELOP RESEARCH EXPERTISE. A SERIES OF NIH AWARDS, CALLED CAREER DEVELOPMENT AWARDS, PROVIDE RESEARCH DEVELOPMENT OPPORTUNITIES TO QUALIFIED INDIVIDUALS WITH DEMONSTRATED RESEARCH POTENTIAL. TWO MECHANISMS HAVE BEEN PARTICULARLY SUCCESSFUL IN THE ATTRACTION OF PHYSICIANS--THE CLINICAL INVESTIGATOR AWARD AND THE SPECIAL EMPHASIS RESEARCH CAREER AWARD. BOTH PROVIDE FOR 3-5 YEARS OF SUPERVISED RESEARCH DEVELOPMENT IN AREAS OF IMMEDIATE INTEREST TO THE FUNDING INSTITUTE. THEY PROVIDE UP TO $30,000 PER YEAR IN SALARY PLUS COMMENSURATE FRINGE BENEFITS AND SOME MODEST AMOUNT OF RESEARCH SUPPORT. THESE PROGRAMS HAVE BEEN SUCCESSFUL AND THUS HAVE DEMONSTRATED A POTENTIAL FOR EXPANSION.

THE NEWEST ADDITION TO THE CAREER DEVELOPMENT AWARD SERIES WAS ANNOUNCED THIS JULY. THIS "PHYSICIAN-SCIENTIST" AWARD IS DESIGNED TO PROVIDE FIVE YEARS OF PHASED SUPERVISED RESEARCH TRAINING. THE FIRST 2-3 YEARS WILL BE UNDER THE GUIDANCE OF A SPONSOR WHO IS A BASIC SCIENTIST. THE AWARD WILL CARRY A SALARY COMPARABLE TO THAT EARNED BY A MEMBER OF THE INSTITUTION'S HOUSE STAFF WITH EQUIVALENT EXPERIENCE, AND $10,000-$20,000 FOR RESEARCH COSTS. THE PROGRAM WILL BE SPONSORED BY SEVEN NIH INSTITUTES. IT COMPLEMENTS THE MSTP PROGRAM IN PROVIDING GRADUATE SCHOOL LEVEL EXPERIENCE FOR THE PROFESSIONAL DEGREE HOLDER WHO BEGINS AT A POST-MEDICAL SCHOOL STAGE.

BUT THE WISDOM OF UNDERTAKING RESEARCH TRAINING COULD EASILY BE QUESTIONED BY A YOUNG PHYSICIAN IF THE OPPORTUNITY TO ENGAGE IN SUPPORTED RESEARCH IN THE FUTURE IS HIGHLY UNCERTAIN. ONE MAJOR FACTOR IMPACTING UPON A YOUNG PHYSICIAN'S DECISION IS HIS OR HER PERCEPTION OF THE LONG-TERM STABILITY OF FEDERAL SUPPORT OF RESEARCH. THIS IS ONE REASON FOR NIH'S CONTINUED EMPHASIS ON THE NEED TO "STABILIZE" OUR OFFERING OF GRANTS FOR INVESTIGATOR-INITIATED PROJECT RESEARCH--TO PROVIDE A REASONABLE DEGREE OF ASSURANCE ABOUT FUTURE OPPORTUNITIES. THE POLICY OF FUNDING A MINIMUM OF 5,000 NEW AND COMPETING AWARDS HAS HELPED, WE BELIEVE, TO STABILIZE EMERGING RESEARCH CAREERS. CURRENTLY 50 PERCENT OF NEW AWARDS AND 10 PERCENT OF ALL AWARDS ARE MADE TO FIRST-TIME APPLICANTS, NOT BY ALLOCATION BUT ON THE BASIS OF OPEN COMPETITION.

WHILE NIH PROGRAMS AND POLICIES WILL UNDOUBTEDLY HAVE A MAJOR IMPACT UPON THE FUTURE OF CLINICAL INVESTIGATION IN THIS COUNTRY, MAINTENANCE AND GROWTH OF THIS FIELD IS THE OBLIGATION OF ACADEMIC MEDICINE, THE MEDICAL PROFESSION AS A WHOLE, INDUSTRY, AND OTHER PARTS OF THE PRIVATE SECTOR, AS WELL AS GOVERNMENT. SOME MEDICAL SCHOOLS--FOR EXAMPLE, DUKE UNIVERSITY, UNIVERSITY OF PENNSYLVANIA, AND OTHERS--HAVE DEVELOPED CURRICULA WITH THE ASPIRING CLINICAL INVESTIGATOR IN MIND. MT. SINAI HAS ALSO MADE MAJOR CONTRIBUTIONS IN TRAINING CLINICAL RESEARCHERS. PRIVATE SECTOR ENTITIES SUCH AS THE AMERICAN CANCER SOCIETY AND THE AMERICAN HEART ASSOCIATION HAVE ESTABLISHED SPECIAL AWARDS FOR PHYSICIAN SCIENTISTS. ALL OF THESE EFFORTS CONTINUE TO MITIGATE THE CIRCUMSTANCES WHICH SEEM TO BE HINDERING THE GROWTH OF CLINICAL INVESTIGATION.

IN ITS UNIQUE WAY, THE LITA ANNENBERG HAZEN AWARD-- WHICH IS ADMINISTERED BY MT. SINAI AND IS ABOUT TO BE AWARDED FOR 1983 NEXT MONTH--IS A STRONG AND ELOQUENT STATEMENT ON THE IMPORTANCE OF CLINICAL INVESTIGATION. THE RECOGNITION AND ENCOURAGEMENT IT GIVES ARE BOUND TO HAVE A POSITIVE EFFECT AT A TIME WHEN THERE IS WIDESPREAD CONCERN ABOUT THE DIFFICULTY OF RECRUITING AND RETAINING PHYSICIANS FOR RESEARCH CAREERS.

THE CURRENT GENERATION OF CLINICAL INVESTIGATORS HAS A SPECIAL RESPONSIBILITY TO PORTRAY THE SATISFACTIONS THAT CAN COME FROM CLINICAL RESEARCH AS A CAREER. WE NEED TO LET STUDENTS KNOW THAT IN CLINICAL RESEARCH THERE IS OPPORTUNITY TO BE A CAPABLE AND CARING CLINICIAN, AND ALSO TO SHARE IN THE EXCITEMENT THAT COMES FROM DISCOVERY.

BEYOND THE PERSONAL GRATIFICATION THAT COMES FROM CREATIVE WORK, CLINICAL RESEARCH OFFERS THE CHANCE TO CONTRIBUTE BOTH TO THE HEALTH OF INDIVIDUAL PATIENTS, AND OF GROUPS OF PEOPLE. WE MUST KEEP STRESSING THAT FOR THOSE EXCEPTIONAL STUDENTS WHO WILL TAKE ON THE CHALLENGE OF RESEARCH, THE REWARDS ARE GREAT.

IN HIS BOOK, "EXCELLENCE: CAN WE BE EQUAL AND EXCELLENT TOO?", JOHN GARDNER REMARKED THAT THE INFLUX OF EXCELLENT NEW PEOPLE INTO A GIVEN FIELD IN LARGE PART DEPENDS UPON THE MORALE OF THAT FIELD.[6] AND A MAJOR COMPONENT OF OUR COLLECTIVE MORALE IS THE OPTIMISM AND ENCOURAGEMENT WE PORTRAY TO NEWCOMERS AND THOSE ON THE BRINK OF DECISION.

I HOPE I HAVE MADE A CONTRIBUTION TO OPTIMISM THIS AFTERNOON IN CITING THE CONTINUING COMMITMENT OF NIH TO THE DEVELOPMENT OF CLINICAL INVESTIGATION, THROUGH THE GCRC'S AND OTHER MEANS.

FOOTNOTES

[1]Conference Summary, "Clinical Investigations in the 1980s; Needs and Opportunities," June, 1981, National Institute of Medicine, National Academy Press, p. 2.

[2]As above, pp. 8-13.

[3]Janet Cuca, "NIH Grant Applications for Clinical Research: Reasons for Poor Ratings or Disapprobal," Division of Research Grants, NIH, September 1982.

[4]Charles R. Sherman, Ph.D., and Thomas E. Morgan, M.D. "Education Patterns and Research Grants Success of Medical School Faculty." An evaluation study prepared for the NIH by the Association of American Medical Colleges, January 1979.

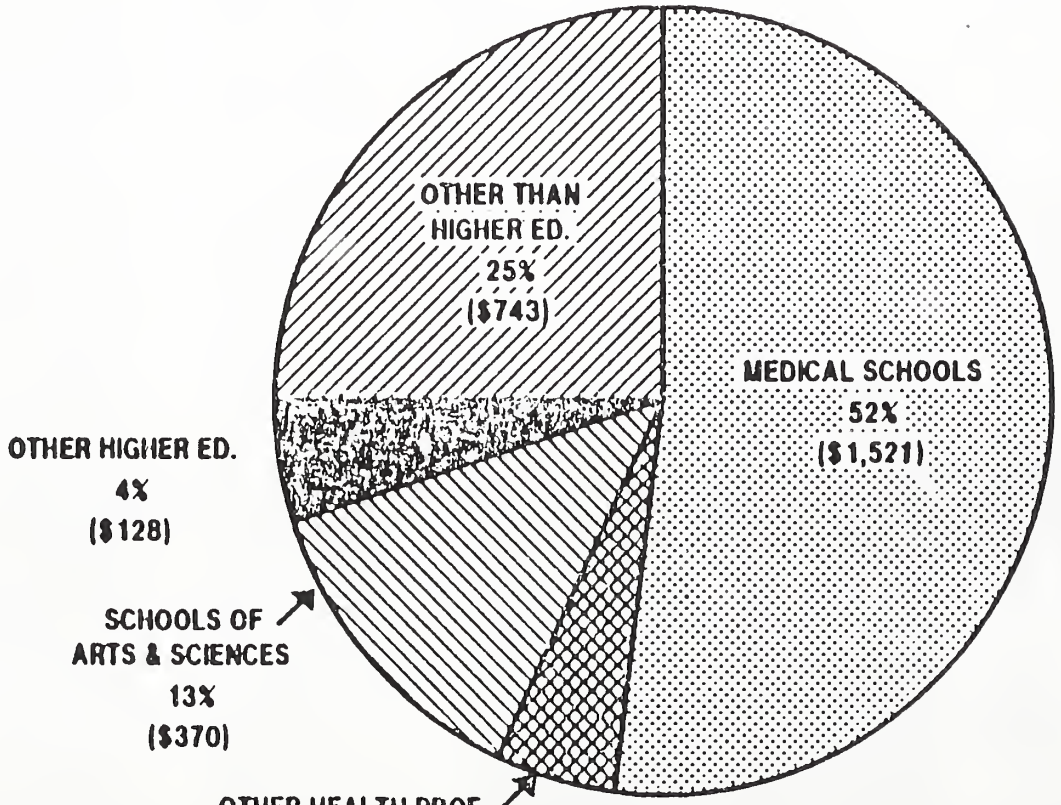
[5]Office of Program Analysis Note No. 6, "Competing Grant Applications from NRSA Trainees," Office of Program Planning and Evaluation,

[6]John W. Gardner, "Excellence: Can We Be Equal and Excellent Too?" Harper & Row, Publishers, New York and Evanston, 1961.

SLIDE 1

MEDICAL SCHOOLS RECEIVE 52% OF ALL NIH AWARDS, FISCAL YEAR 1982

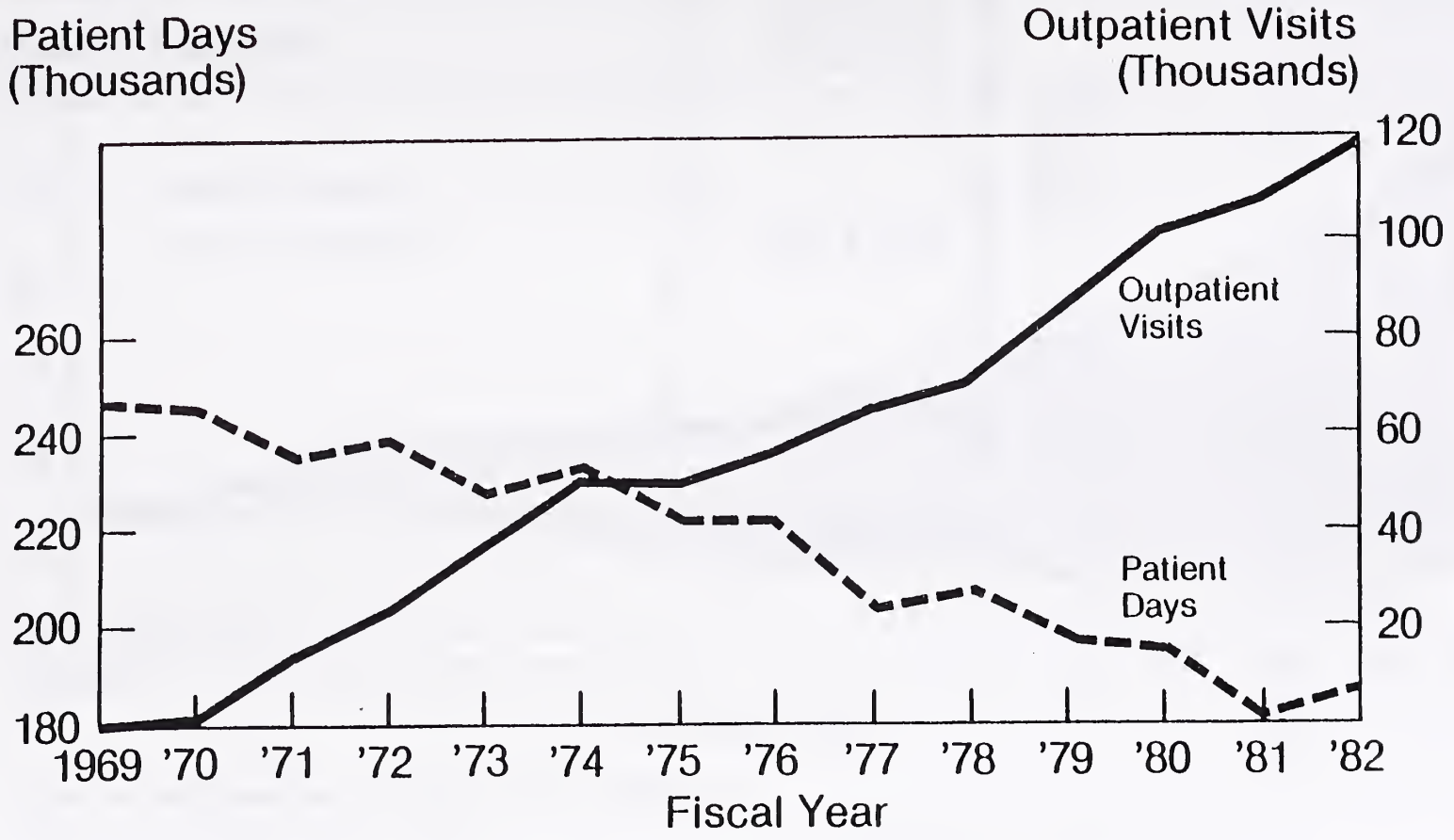
(CURRENT DOLLARS IN MILLIONS)


OTHER THAN HIGHER ED. 25% ($743)
MEDICAL SCHOOLS 52% ($1,521)
OTHER HIGHER ED. 4% ($128)
SCHOOLS OF ARTS & SCIENCES 13% ($370)
OTHER HEALTH PROF. 6% ($167)
FY 1982
$2,930 MILLION

SOURCE: NIH, DRG, STATISTICS AND ANALYSIS BRANCH

SLIDE 2

GCRC Patient Days and Outpatient Visits, FY 1969-1983



Source: GCRCP/DRR/NIH, October 11, 1983.

SLIDE 3

GCRC PROGRAM, FY 1970-1982
(Dollars in Thousands)

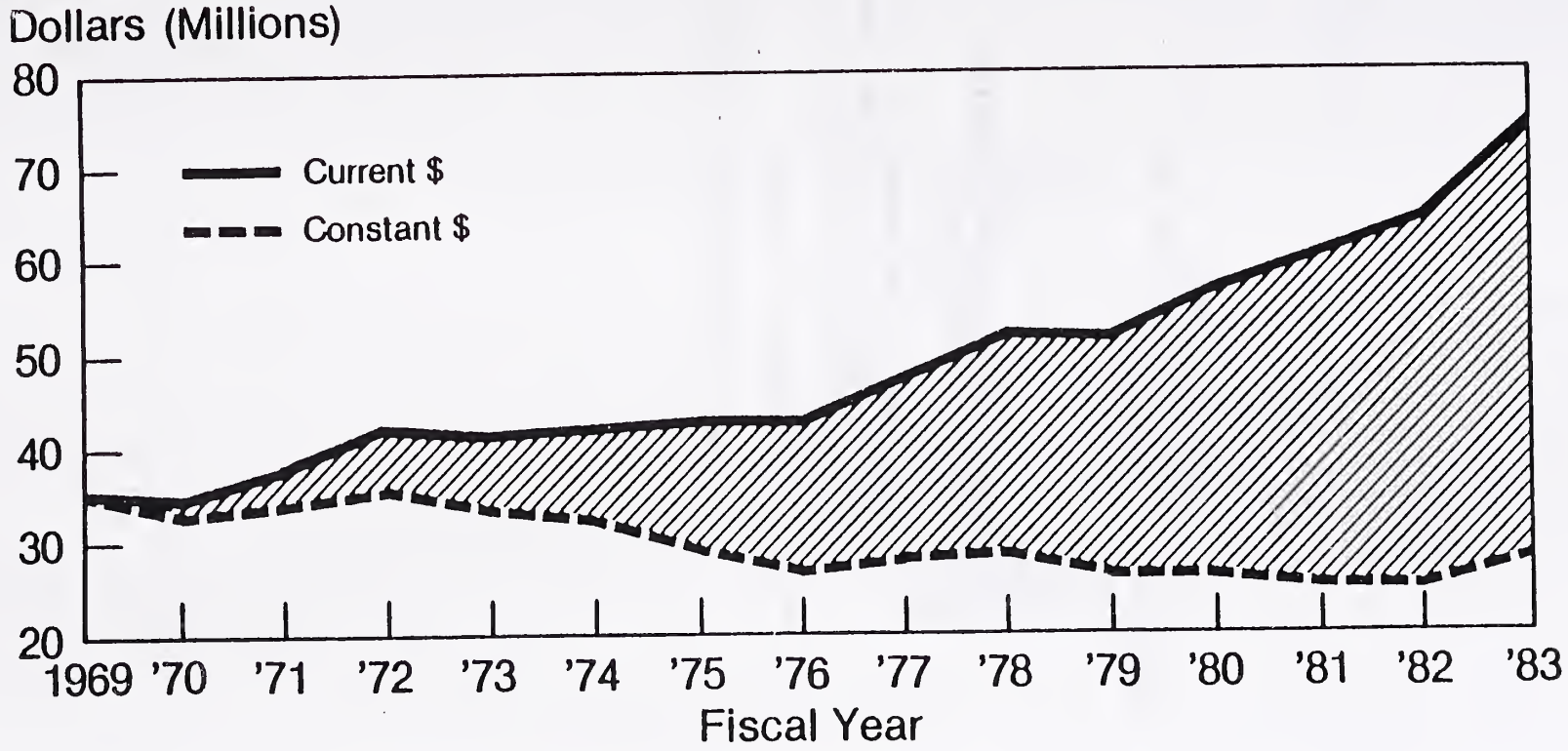
FY	Centers	Funded beds	Apportionment
1970	93	904	$ 35,004
1972	84	907	42,181
1974	87	877	42,320
1976	84	784	42,533
1978	79	633	51,946
1980	75	602	56,218
1982	74	595	64,384

Source: GCRCP/DRR/NIH, 10/11/83.

SLIDE 4

General Clinical Research Centers Program, FY 1969-1983

In Current and Constant Dollars* (Millions)



*Based on the Biomedical R&D Price Index FY 1969 = 100.

Source: GCRCP/DRR/NIH, October 11, 1983.

SLIDE 5

GENERAL CLINICAL RESEARCH CENTERS
WERE USED IN FY 1982 BY

3,939 Investigators conducting
3,460 Projects supported by more than
2,000 NIH grants and contracts

Source: GCRCP/DRR/NIH, 10/11/83.

SLIDE 6

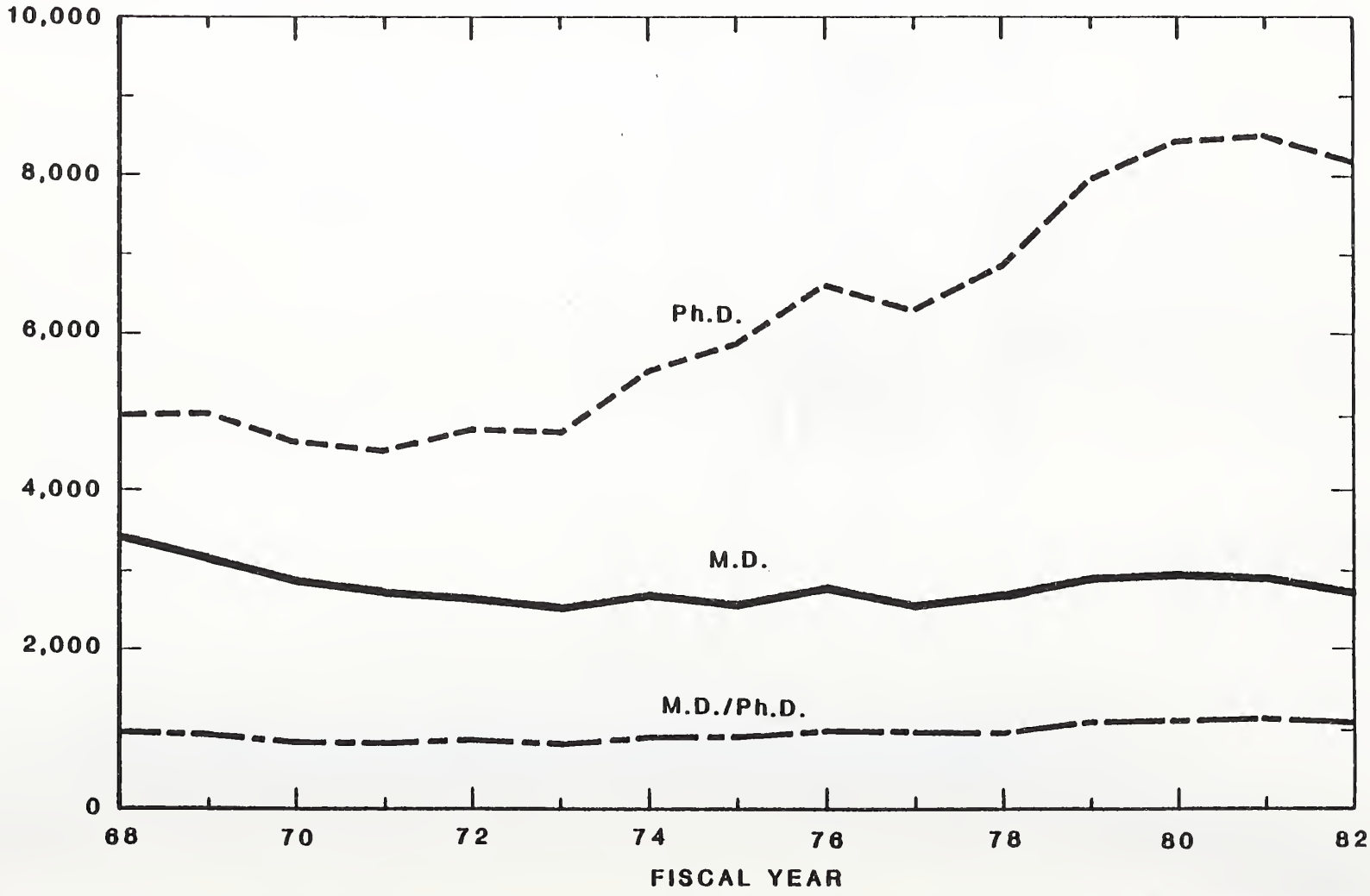
GCRC SUPPORT FOR
SOME TRANS-NIH CATEGORIES, FY 1982
(In Thousands)

Arthritis	$ 2,280
Cystic fibrosis	419
Diabetes	12,900
Digestive diseases	10,055
Epidemiology	2,100
Immunology	6,500
Nutrition	11,500

Source: GCRCP/DRR/NIH, 10/11/83.

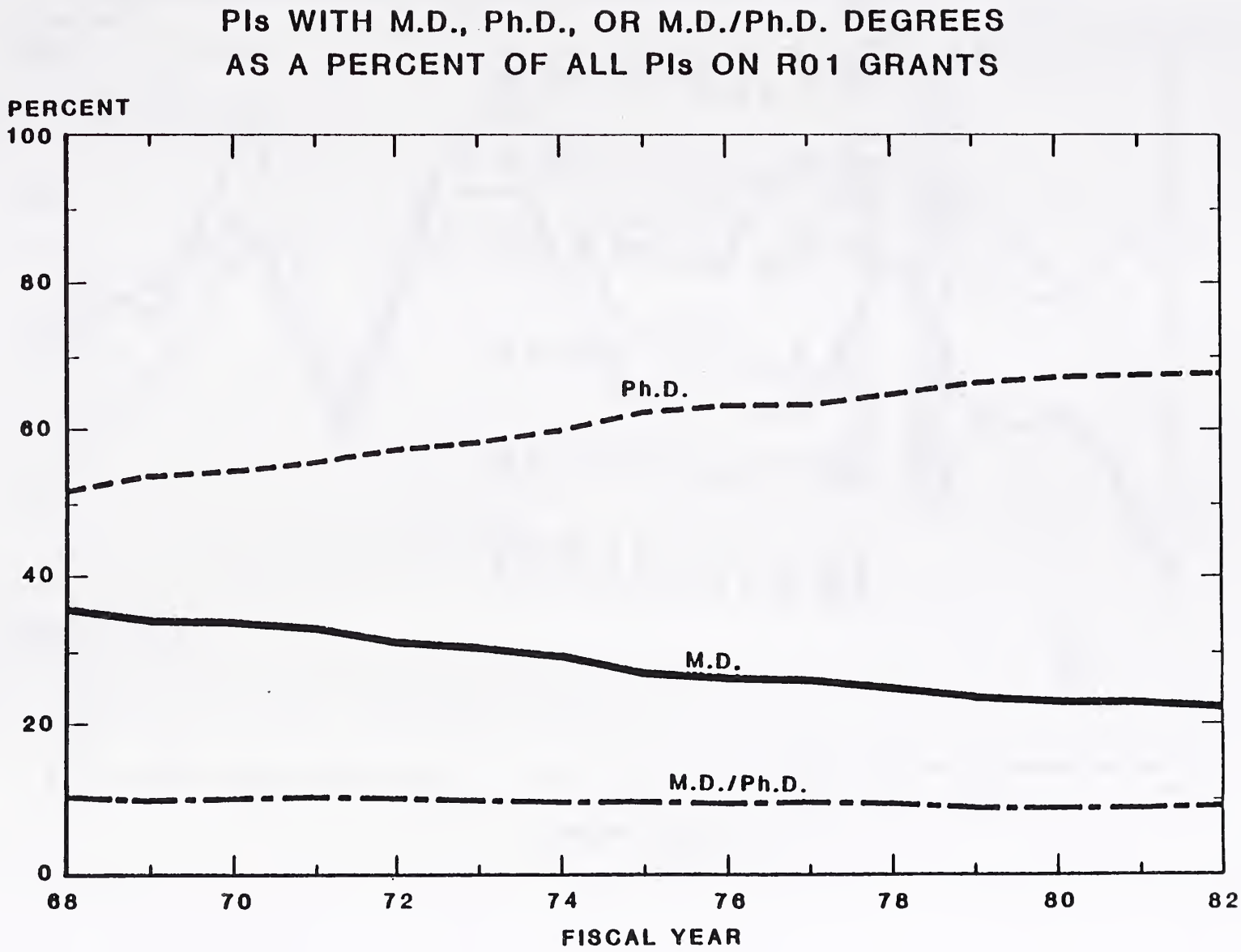
SLIDE 7

NUMBER OF PIs WITH M.D., Ph.D., OR M.D./Ph.D. DEGREES ON ALL R01 GRANTS



Source: RAEB/DRG/NIH.

SLIDE 8

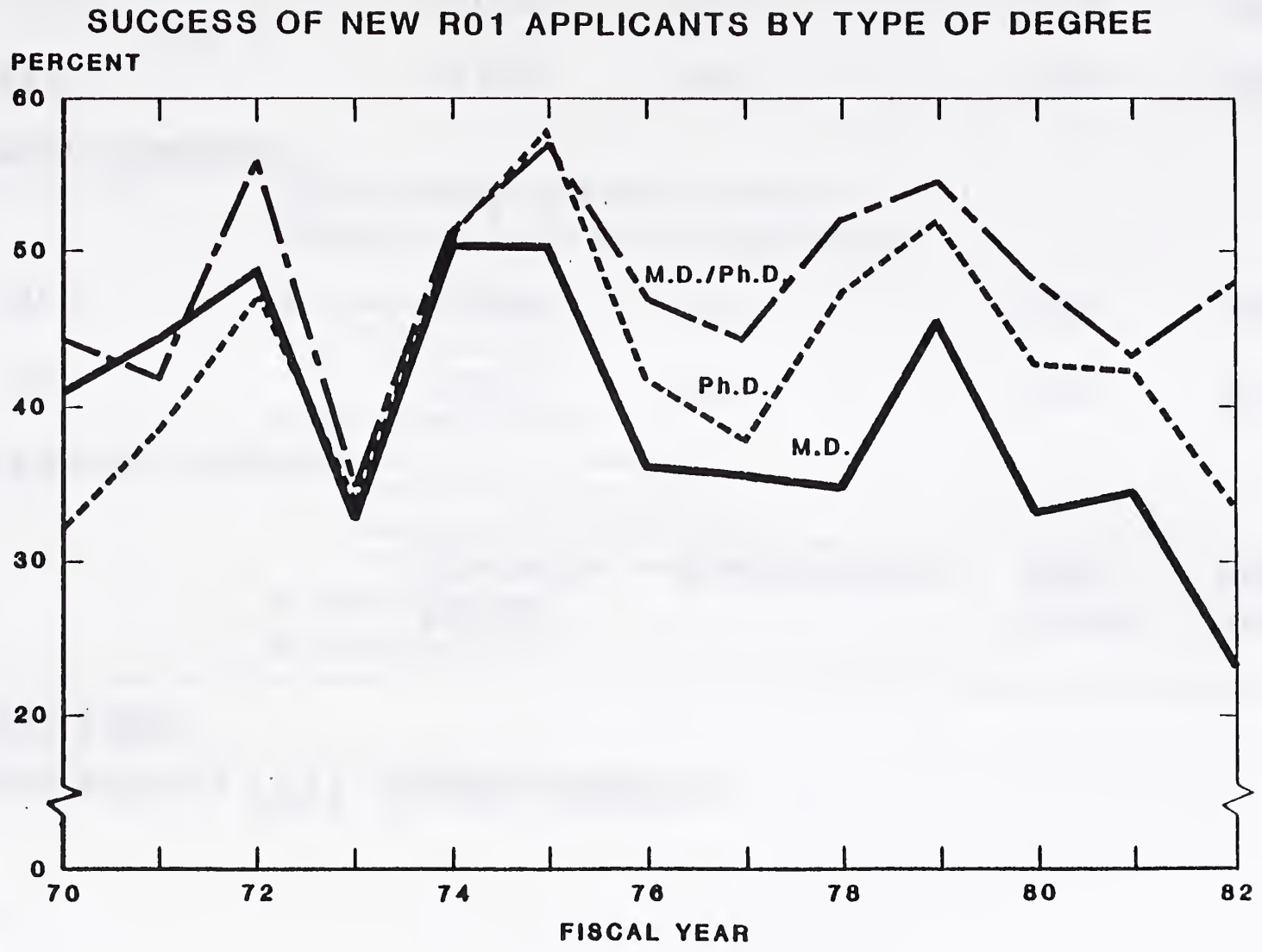

PIs WITH M.D., Ph.D., OR M.D./Ph.D. DEGREES
AS A PERCENT OF ALL PIs ON R01 GRANTS
PERCENT
100
80
60
40
20
0
Ph.D.
M.D.
M.D./Ph.D.
68
70
72
74
76
78
80
82
FISCAL YEAR

SLIDE 9

APPROVAL, AWARD, AND SUCCESS RATES FOR COMPETING R01 APPLICATIONS, 1974-82

Fiscal year	Approval rate		Award rate		Success rate	
	M.D.	Ph.D.	M.D.	Ph.D.	M.D.	Ph.D.
1974	72%	76%	60%	56%	43%	43%
1975	72	76	60	60	43	46
1976	68	73	50	46	34	34
1977	71	75	41	37	29	28
1978	74	79	45	45	33	36
1979	76	78	50	52	38	40
1980	76	80	42	42	32	33
1981	80	83	40	38	32	32
1982	83	85	34	34	29	29

SLIDE 10


SUCCESS OF NEW R01 APPLICANTS BY TYPE OF DEGREE
PERCENT
60
50
40
30
20
0
M.D./Ph.D.
Ph.D.
M.D.
70
72
74
76
78
80
82
FISCAL YEAR

SLIDE 11

Competing R01 Applications 1976-1981

	Number Reviewed	Recommended	Award Rate	Success Rate
No Human Subjects:				
— M.D.	10,552	73%	42%	31%
— Ph.D.	40,815	74%	40%	30%
Human Subjects:				
— M.D.	12,166	64%	39%	25%
— Ph.D.	12,078	61%	38%	23%

SLIDE 12

Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

- Research Problem:
  - — Hypothesis (47%)
  - — Significance (30%)
- Experimental Design:
  - — Study Group or Controls (40%)
  - — Technical Methodology (66%)
  - — Data Collection Procedures (41%)
  - — Data Management and Analysis (31%)
- Investigator (17%)
- Resources (4%)

SLIDE 13

AVERAGE SUCCESS RATES ON NIH COMPETING RESEARCH GRANT APPLICATIONS

By Doctoral Degree and NIH/PHS Training Support*
FY 1967-78

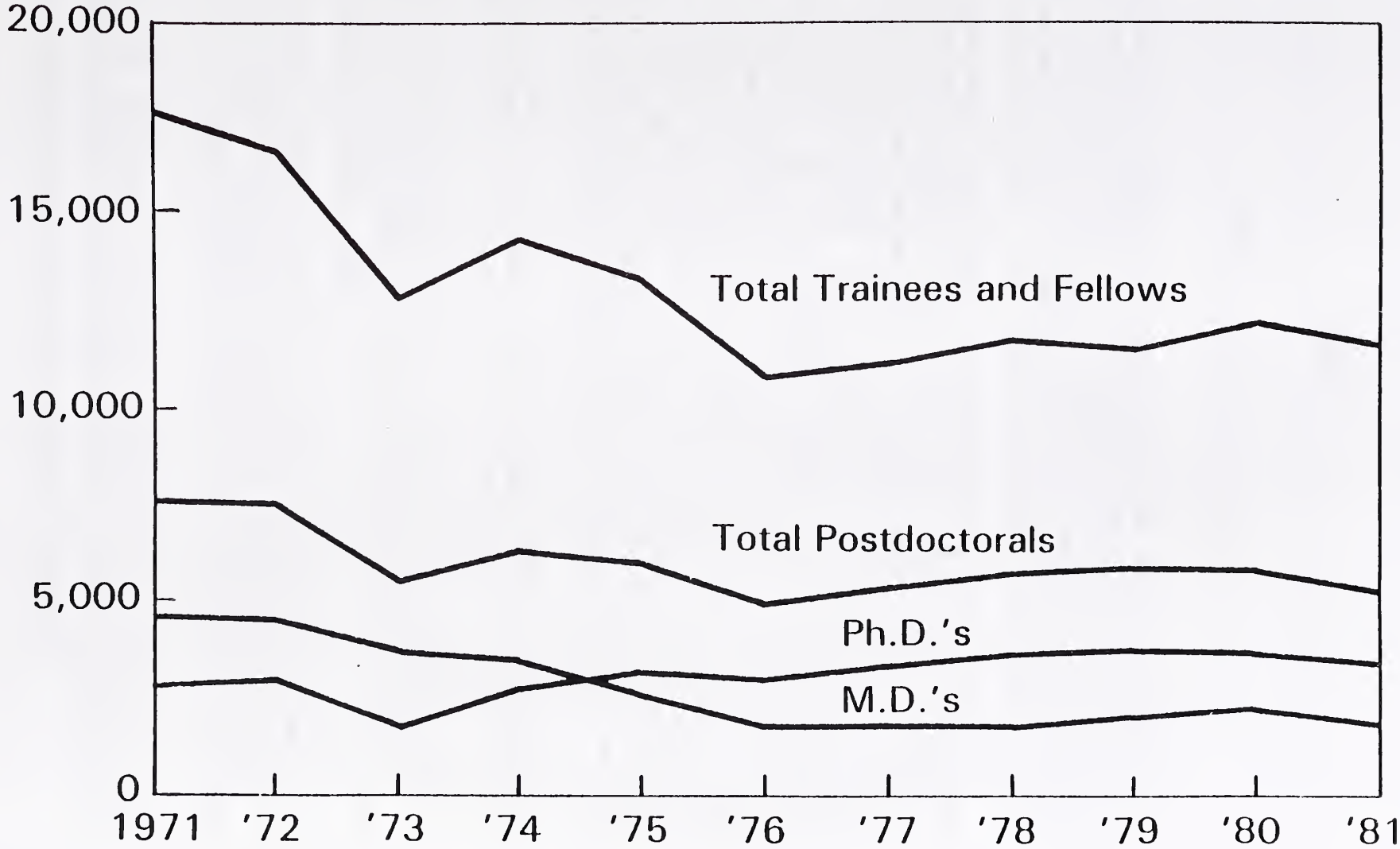
Doctoral degree	Success rates	
	With training support	Without training support
M.D. or equivalent	36.5%**	25.0%**
Ph.D. or equivalent	37.9**	27.1**
Professional & academic (e.g., M.D./Ph.D.)	40.4	29.4
Other professional doctorates	41.7	27.6

*Based on five percent random sample of NIH Grant Applicant Summary File, which includes R, P, M, and S grants. Success rate is the ratio of funded competing research grant applications to all such applications multiplied by 100.

**Significantly different at <.01 level.

SLIDE 14

TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81



REMARKS*

by

James B. Wyngaarden, M.D.**

When John Potts approached me about saying a few words at this evening's reunion I was happy to accept. As a House Officer at the MGH in 1948-51, I was a frequent user of the Treadwell in its Hellenic-Colonial period in the Moseley Building. The opportunity to do something for the Treadwell in return instantly struck a responsive chord, particularly since in my present position I travel as much as I possibly can. As you know, it is harder to hit a moving target.

For some reason, the Treadwell Library always symbolized for me the linkage of the MGH with great figures of the historic past. I often mused that I was searching the stacks, particularly the second floor stacks, as Oliver Wendell Holmes had done decades before. I did not know until this morning that the Treadwell Library was not moved from the Bulfinch to the Moseley until 22 years after Holmes' death. In preparation for this talk, I searched Elinor Tilton's biography of Holmes, The Amiable Autocrat, to see whether there was any reference to his use of the Treadwell. There is a reference to Treadwell, but I am not sure it has anything to do with the Library. In 1856 a William Treadwell offered $50,000 to Harvard University to endow a chair in anatomy and physiology, but tied the bequest to a condition clearly a criticism of Holmes, for he stipulated that the holder of the professorship was on no account to be allowed to lecture before the Lowell Institute, Lyceums, or other establishments for amusing the public. The Harvard Corporation having no reason at all to be dissatisfied with its Parkman Professor, who was known for his conscientiousness and excellence as a teacher, refused the legacy, but Holmes was stung by the criticism and began to cancel engagements and refuse others.

Two years later, Dr. John G. Treadwell of Salem donated his books and $5,000 for purchases of new books, and the Treadwell Library was established in the Bulfinch Building. As it turns out, these two Treadwells are unrelated.

Some time after John Potts' call, I received a letter from Henry Mankin, confirming the invitation and adding that I should also include a low-key exhortation of my fellow members of the House Pupils Association to give generously to the Library. I have an idea on how to do this, but I will save it for the end of my brief remarks.

The Treadwell Library is 125 years old this year, but the problems faced by health professionals in trying to keep abreast of published new developments go back much further. John Mayow, in 1668, wrote: "Disease, as it stalks through the land, cannot keep pace with the incurable vice of scribbling about it."

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* Presented on the Occasion of the 125th Anniversary of the Treadwell Library, Massachusetts General Hospital, October 28, 1983, in Boston, Massachusetts.

** Director, National Institutes of Health, Bethesda, Maryland.

In Ecclesiastes we read, "of the making of many books there is no end. And much study is a weariness of the flesh." That was written B.C. -- before computers.

In The Second Career, "Neurosurgery--Yesterday, Today and Tomorrow," Wilder Penfield wrote, "The Egyptians made a fatal mistake. They wrote textbooks, the hermetic books. They made another and more serious mistake, and that was to believe that the textbooks were correct. So they forbade physicians, at peril of their lives, to depart in any way from the treatment prescribed in the hermetic books. It was a remarkable experiment. . . . The experiment demonstrated that standardization can halt advance but it does not in any way hinder retrogression."

A contrary opinion was expressed a century ago by Theodor Billroth in The Medical Sciences in the German Universities. There he states, "It is a most gratifying sign of the rapid progress of our time that our best text-books become antiquated so quickly." Billroth, so far as I know, was not Egyptian.

Libraries, by tradition and etymology, have been concerned with books. Increasingly, however, we view libraries not as warehouses of the printed word, but as providing access to information. This information may be in books and journals, but it may also be in microfilm, videocassettes, videodiscs, and in computer files. Let me take just a minute to acquaint you with several exciting, near-term applications of communications technology.

The first has to do with that most basic and traditional library function --archival storage. It will soon be possible to achieve "prospective preservation"--that is, capturing and storing the printed literature in machine-readable form in a permanent medium at the time of publication, rather than waiting until after damage by flood, mold, bookworms, or more likely, until after the inevitable deterioration of the paper has become evident. One videodisc will store 100,000 pages of text, or the total annual output of some 100 scientific journals, or 40 copies of The Cecil Textbook of Medicine, Wyngaarden and Smith edition.

A second application is what is called demand publication, by which we mean the ability to retrieve documents stored in a digital form and reprinted on demand with a quality comparable to the original.

Another is the electronic journal--those that will exist and be delivered exclusively in an electronic format. A number of important scientific publishers are now experimenting with this, driven by the seemingly inexorable rise in publishing costs. As electronic access becomes more common, the number of traditional journals on paper will decrease, behooving users as well as librarians to learn how to search the new electronic publications. The advent of electronic journals will pose some interesting problems for indexing, copyright ownership, and the traditional concept of library services.

The delivery of randomly accessible graphics via optical videodiscs is another potential application. Such graphics capability will make feasible the concept of online encyclopedias that contain not only text, color plates, and halftones, but also randomly accessible audiovisual motion sequences under the control of the viewer. It will provide a powerful new approach for health-science education, for example, in teaching radiology and those content areas that require the use of a microscope.

There is the exciting possibility of replicating billions of characters of scientific information on digitally encoded optical discs and then providing low cost copies to local, regional, and national information centers. At the present time it costs about $2500 to produce a master disc; copies can be made in quantity for about $10 per disc. One potential application of this technology would allow the entire MEDLINE file (some 800,000 references from the last three to four years) to be stored on two or three videodiscs. The databases could then be made available inexpensively for use on equipment at local institutions, obviating the need to pay telephone line charges to search and retrieve references from a remote central computer.

Although the forms in which we store biomedical information may be changing, the uses to which we put it remain unchanged, namely, for research, health care, and education. The needs in these areas are similar but not necessarily congruent.

Researchers, for example, can frequently be satisfied only with the most exhaustive search of the literature. A MEDLINE Search that turns up 300 references does not faze them a bit. In fact, they are likely to ask the librarian if translations are available for the foreign language articles!

The obvious reason for the researcher's frequent insistence on comprehensiveness is that, in a specialized field, one must constantly be aware of previous related studies and the current work of peers. An article published by a scientist half-way around the world may contain a useful clue that can be applied to one's own work.

Contrast the scientist's desire for comprehensiveness with the need of the health practitioner for just two or three pertinent articles from available journals. The practicing physician is likely to want a rapid review of the literature to help with a particular problem. Whereas the scientist or scholar may tolerate delay in receiving documents, the practitioner with a patient to care for wants information at once and the modern library must be prepared to serve these requirements expeditiously.

The third major use of biomedical libraries is for health science education. In this area, audiovisual materials are sometimes of equal importance with books and journals.

The library of a unique institution like MGH must be prepared to serve all these needs, and the Treadwell Library certainly does this with distinction. Your librarian, Jackie Bastille, is one of the most dynamic and successful directors in the country. As a result of her leadership, the Treadwell's collections have been expanded, the facilities renovated, and the services modernized.

In this you are somewhat more fortunate than Dr. Westphal, your fictional television colleague who labors across town at St. Elsewhere. If you have ever seen his office you will have noticed the issues of Index Medicus piled on the shelf behind his desk.

St. Elsewhere is not yet a MEDLINE user, but the Treadwell has been a long-time MEDLINE center and your staff have frequent recourse to it. As you

know, MEDLINE is a service of our National Library of Medicine, whose staff, incidentally, send their best to their colleagues at the Treadwell.

The NLM administers a grant program under the Medical Library Assistance Act and I was impressed to learn that over the years more than 1,000 U.S. medical libraries have received funding under the Act. I was amazed to learn, however, that the Treadwell Library has not been a recipient of a grant from NLM. Although these are lean times for all Federal agencies, let me assure you that there are grant funds that can be made available to improve medical library resources and services.

Infinitely more important than any outside funds is the commitment made by the parent institution and the actual users of the Library. Today's program is ample evidence of such a commitment. I hope that my remarks about the value of a medical library have persuaded you--if you needed pursuasion--that no aspect of your professional life is more worthy of support than a medical library; and no library is more worthy of your support than the Treadwell Library.

I told Henry Mankin that if my "low-key exhortation" was not productive he might give me the names of MGH House Pupils who are past, present, and potential applicants for NIH grant support. Our computerized grant file has a long memory.

Mark Twain observed that it is an easy matter to resolve to do good; it is even easier to exhort others to do good and no trouble. So, let me urge all of you to give generously to the Treadwell!

Thank you.

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

I am pleased to welcome you here this morning as you begin the task of planning for a National Symposium on Laboratory Animal Welfare to be sponsored by the National Institutes of Health (NIH) next Spring. This symposium and the educational sessions that will follow it rank among the most important new programs that NIH will undertake in the next year.

I do not need to justify to this audience the fact that medical research cannot continue to progress without the use of laboratory animals. While it is true that computer modeling and procedures in vitro can replace animals in some toxicological testing, the involvement of animals to demonstrate the response of biological systems and organisms to carefully measured interventions is and will remain central to the research enterprise.

The Public Health Service (PHS) promulgated its first policy for the protection of human research subjects in 1966. That policy has been revised and expanded in the context of public debate many times in the 17 years of its existence. The research community, the Congress and the public have all contributed to its development.

The human subjects protections now in place reflect a broad public consensus of all parties concerned with the rights and welfare of human research subjects.

The Animal Welfare Policy of the PHS is older than the policy for protection of human subjects. The first edition of the Guide for the Care and Use of Laboratory Animals was published in 1963, and it has been revised four times since then. It is currently undergoing its fifth revision.

The recommendations contained in the Guide coupled with the NIH Principles for Use of Animals reflect a consensus within the scientific community, but they do not yet represent a consensus of those numerous groups and associations concerned with animal welfare. In recent years we have witnessed increasing criticism of the involvement of animals in research. This criticism has been reflected in the 97th Congress which has considered no less than five legislative initiatives concerning the use of animals in research.

NIH has received more than 1,500 letters conerning the case of Dr. Edward Taub. That matter is still under appeal within the Department more than two years after Dr. Taub was charged by the State of Maryland with cruelty to

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* Presented to the Advisory Group Meeting for Planning a National Symposium on Animal Welfare, National Institutes of Health, October 31, 1983.

** Director, National Institutes of Health, Bethesda, Maryland.

research animals. Letters continue to arrive every day concerning Dr. Taub's research. No charge of noncompliance with human subjects regulations has ever generated as much public concern as the charge of mistreatment of 16 subhuman primates.

The possible erosion of public support for our policies for humane care and use of laboratory animals is a matter of deep concern. The critics of our policies appear to us to be sincere and politically sophisticated. It is, therefore, incumbent on us to strive to build a wider consensus concerning the policy for the humane care and use of laboratory animals. It no longer suffices to have a policy which represents a consensus of the research community. If medical research is to continue to enjoy solid public support, then the policy must be explained and defended in a wider context than ever before.

The symposium which is now in the planning phase is central to our effort to build a broad public consensus for appropriate policies for the use of animals in research.

Let me thank you for your contribution to this important issue and join with you in pledging my full support for your efforts.

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

Professor Arseni, Professor Moraru, and other Members of the Romanian delegation.

It is an honor for me to welcome you to the National Institutes of Health for this Third United States-Romania Workshop on Biomedical Research devoted to the topic of Basic Cancer Research. You have made a long journey and are no doubt still trying to recover from "jet lag." We are sorry to put you to work so soon. However, in looking over the impressive program I am sure that your visit will be well worth the effort you have made.

I would like also to welcome our American scientists from out-of-town who are giving willingly of their time and expertise to join us.

The group here this morning and for the workshop ahead is purposefully small--to provide maximum opportunity for the sharing of scientific information in basic cancer research. We hope that this workshop will serve to stimulate a dialogue which will continue over the months and years to come, not only among those participating here today but also among other colleagues in your laboratories who were not able to be with us. Furthermore, I do not view us as two separate groups--U.S. scientists and Romanian scientists--but rather as a single group without respect to nationality, sharing common backgrounds, purposes and objectives in addressing the important area of basic cancer research for both our countries and mankind.

Allow me to express a particular and personal welcome to Professor Arseni as President of the Romanian Academy of Medical Sciences. As leaders of our respective government agencies supporting biomedical research, we have much in common--especially the problems of seeing that the maximum amount of high quality science is accomplished within the limitations of our resources. I hope, and am sure, that this workshop will demonstrate once again that sharing knowledge and coordinating research yields advances in science and avoids duplication or misguided research, and thus benefits us all. Professor Arseni, I hope you will have ample opportunity to become acquainted with NIH in these few days and also that you will have reasons for visiting us again in the future.

Let me again express to all of you a most sincere welcome to NIH, whether you have been here before or for the first time, and thank you for coming together for this most useful cooperative purpose. Best wishes for a successful workshop.

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* Presented before the Third U.S.-Romania Workshop on Biomedical Research, National Institutes of Health, October 31, 1983.

** Director, National Institutes of Health, Bethesda, Maryland 20205.

PRESERVING THE SCIENTIFIC ENTERPRISE*

BY

JAMES B. WYNGAARDEN, M.D.**

MANY OF YOU HAVE BEEN PARTISANS OF THE NATIONAL INSTITUTES OF HEALTH AS LONG AS I HAVE. BECAUSE OF THAT, I THINK YOU WILL APPRECIATE AS MUCH AS I DO A RECENT STATEMENT BY AMERICA'S PREMIER BIOLOGY WATCHER, LEWIS THOMAS. IT IS FROM THE FOREWORD BY DR. THOMAS FOR A SOON-TO-BE PUBLISHED VOLUME WHOSE CHAPTERS WERE WRITTEN BY FORTY LEADING SCIENTISTS ABOUT THEIR YEARS IN THE NIH LABORATORIES.

DR. THOMAS COMMENTED, "WE SEEM TO BE LIVING THROUGH A PERIOD (TRANSIENT, I HOPE) OF PUBLIC DISILLUSION AND DISCOURAGEMENT OVER GOVERNMENT AND ALL ITS WORKS. AT ALL LEVELS, BUREAUCRACY IN GENERAL IS MISTRUSTED, HERE AND ABROAD. THE WORD IS OUT THAT GOVERNMENT DOESN'T REALLY WORK, CAN'T GET THINGS RIGHT, WASTES PUBLIC MONEY, FUMBLES ALONG, STALLS, GETS IN THE WAY.

"AT SUCH A TIME, IT LIFTS THE HEART TO LOOK CLOSELY AT ONE INSTITUTION CREATED BY THE UNITED STATES GOVERNMENT

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*Address at the Annual Meeting of the Association of American Medical Colleges, November 7, 1983.

**Director, National Institutes of Health, Bethesda, MD.

WHICH HAS BEEN ACHIEVING, SINCE ITS OUTSET, ONE SPECTACULAR, STUNNING SUCCESS AFTER ANOTHER. THE NATIONAL INSTITUTES OF HEALTH IS NOT ONLY THE LARGEST INSTITUTION FOR BIOMEDICAL SCIENCE ON EARTH; IT IS ONE OF THIS NATION'S GREAT TREASURES. AS SOCIAL INVENTIONS FOR HUMAN BETTERMENT GO, THIS ONE IS A STANDING PROOF THAT, AT LEAST ONCE IN A WHILE, GOVERNMENT POSSESSES THE CAPACITY TO DO SOMETHING UNIQUE, IMAGINATIVE, USEFUL, AND ALTOGETHER RIGHT."[1]

FROM THE PERSPECTIVE OF DECADES, THE DEVELOPMENT OF THE NIH REPRESENTS A REMARKABLE ACCOMMODATION OF THE PUBLIC'S UNDERSTANDABLE DEMANDS FOR RESULTS FROM THE EXPENDITURE OF PUBLIC FUNDS AND SCIENCE'S INHERENT NEED FOR INDEPENDENCE AND ELBOW ROOM.

THE SUCCESSION OF LAWS THAT ESTABLISHED AND MOLDED THE NIH ~~IN A SPECIAL CATEGORY OF~~ WERE WISE, VISIONARY, AND ENORMOUSLY BENEFICIAL ~~ACTION~~S. BUT AS FARSIGHTED AND WISE AS THE ENABLING STATUTES HAVE GENERALLY PROVED TO BE, THE DEVELOPMENT AND MATURITY OF THE NIH RESULTED FROM SURE-HANDED AND ENLIGHTENED ADMINISTRATION OF THE CONGRESSIONAL MANDATES, ACCOMPANIED BY A TOLERANT CONFIDENCE ON THE PART OF CONGRESS THAT ITS INTENTION WOULD BE HONORED.

IT WAS FORTUNATE THAT DURING THE PERIOD OF ITS EXPLOSIVE GROWTH FROM 1955 TO THE LATE 60s, THE NIH WAS DIRECTED BY AN UNUSUALLY ABLE AND STRONG LEADER--JAMES A. SHANNON. JIM SHANNON INSISTED THAT THE CONGRESSIONAL MANDATE TO CONDUCT RESEARCH IN CANCER, HEART DISEASE, AND ARTHRITIS, FOR EXAMPLE, BE INTERPRETED BROADLY. HE REALIZED THAT THE SCIENTIFIC BASE WAS NOT SUFFICIENT TO PERMIT A FRONTAL ASSAULT ON THE DISEASES THEMSELVES. HE SET ABOUT TO BUILD THE RESEARCH CAPABILITY OF THIS COUNTRY THROUGH THE INTRAMURAL PROGRAM AT BETHESDA AND THROUGH A SUBSTANTIAL EXPANSION OF THE MECHANISMS OF GRANTS-IN-AID TO INSTITUTIONS.

THE SHANNON ERA WAS A TIME WHEN YEAR-TO-YEAR BUDGET INCREASES FOR THE NIH AVERAGED AROUND 25 PERCENT. WHAT WAS ENTIRELY FORESEEABLE HAS HAPPENED. ALTHOUGH OUR ANNUAL APPROPRIATION IS NOW WELL OVER FOUR BILLION DOLLARS--TEN TIMES WHAT IT WAS IN 1960--THE INCREASES FOR THE PAST DECADE HAVE BARELY KEPT PACE WITH INFLATION. OUR THOUGHTS HAVE TURNED TO PRESERVATION; THAT IS, THE PRESERVATION OF THE MOMENTUM OF THE BURGEONING BIOMEDICAL RESEARCH ENTERPRISE.

BY 1975, THE NIH APPROPRIATION HAD JUST REACHED TWO BILLION DOLLARS, BUT THE POSITIVE SLOPE OF THE GROWTH CURVE WAS FLATTENING NOTICEABLY. IN ITS REPORT ON THE 1976 NIH

BUDGET, THE SENATE APPROPRIATIONS COMMITTEE WARNED THAT "ANNUAL INCREASES SHOULD NOT BE ROUTINELY EXPECTED AND IT WOULD THEREFORE BE PRUDENT TO DEVELOP A POLICY FOR THE MOST EFFECTIVE MANAGEMENT OF THE RESEARCH GRANT PROGRAMS ON THE BASIS OF RELATIVELY CONSTANT FUNDING FROM YEAR TO YEAR."[2]

AS EARLY AS 1974, THE NIH HAD BEGUN ACCOMMODATING TO A RELATIVELY CONSTANT BUDGET BY FUNDING THE INCREASING NUMBER OF EXCELLENT RESEARCH PROPOSALS THROUGH SHIFTING FUNDS FROM AMONG VARIOUS OTHER PROGRAM MECHANISMS.

THERE WAS A CLEAR NEED FOR ARTICULATION OF POLICY FOR GUIDANCE THROUGH THE UNCHARTED FUNDING PLATEAU. IN 1978, UNDER THE LEADERSHIP OF DON FREDRICKSON AND SECRETARY CALIFANO, A NATIONAL CONFERENCE ON HEALTH RESEARCH PRINCIPLES WAS HELD IN BETHESDA. ITS PURPOSE WAS TO DRAW OUT ~~OF~~ IDEAS FROM THE DEPARTMENT'S HEALTH AGENCIES AND THE RESEARCH COMMUNITY ~~IDEAS~~ FOR A RESEARCH PLAN TO HELP GUIDE IN THE ALLOCATION OF LIMITED RESOURCES. MORE THAN 100 NONFEDERAL SCIENTISTS, MANY OF THEM REPRESENTING MAJOR SEGMENTS OF THE SCIENTIFIC COMMUNITY, PARTICIPATED ACTIVELY IN THE CONFERENCE DISCUSSIONS.

ALL PARTIES TO THE CONFERENCE AGREED ON THE ESSENTIALITY OF THE FEDERAL COMMITMENT TO ENSURE A STRONG "SCIENCE BASE" FOR HEALTH. THEY REPEATEDLY STRESSED THE NEED FOR LONG-TERM STABILITY IN THE FUNDING OF HEALTH RESEARCH AND WARNED THAT PRESENT RESEARCH CAPABILITIES MUST BE SUSTAINED AND ENHANCED TO ASSURE FUTURE HEALTH GAINS.

THESE CONSIDERATIONS STIMULATED THE DEVELOPMENT OF THE SO-CALLED "STABILIZATION STRATEGY" THAT WAS CONCEIVED TO BENEFIT BIOMEDICAL RESEARCH BY STABILIZING THE SCIENCE BASE. AS APPLIED TO RESEARCH PROJECT GRANTS, A MAJOR GOAL WAS TO MINIMIZE SIGNIFICANT OSCILLATIONS IN NIH COMPETING GRANTS AND THEREBY TO PREVENT INVESTIGATORS FROM FORSAKING RESEARCH CAREERS DUE TO THE UNPREDICTABILITY OF SUPPORT.

OVER TIME, AND IN THE HECTIC GIVE AND TAKE OF THE ITERATIVE BUDGET PROCESS, THE ORIGINAL CONCEPT OF STABILIZATION WAS ALTERED AND QUICKLY OVERSIMPLIFIED, SO THAT IT BEGAN TO BE APPLIED ONLY TO RESEARCH PROJECT GRANTS, AT THE EXPENSE OF OTHER SUPPORT MECHANISMS. THE GOAL OF 5,000 NEW AND COMPETING RESEARCH GRANTS BECAME AN END IN ITSELF TO BE MET ~~ONLY~~ BY REPEATED DOWNWARD NEGOTIATIONS IN DIRECT COSTS, AND REDUCTIONS IN OTHER ESSENTIAL PROGRAM ACTIVITIES.

THE PRESENT AND CONTINUED ADHERENCE TO THE ABRIDGED STABILIZATION STRATEGY HAS BECOME PROBLEMATIC IN THAT IT DOES NOT REFLECT A BROAD VIEW OF THE REAL NEEDS OF A TOTAL BIOMEDICAL RESEARCH PROGRAM TO ADVANCE THE GENERATION OF NEW KNOWLEDGE. SERIOUS CONCERNS HAVE BEEN ADVANCED BY NIH INSTITUTE DIRECTORS BY THE NIH DIRECTOR'S ADVISORY COMMITTEE, BY NATIONAL ADVISORY COUNCILS, AND OTHER GROUPS REPRESENTATIVE OF THE RESEARCH COMMUNITY.

WHILE IT IS TRUE THAT NIH HAS SUPPORTED AT LEAST 5,000 NEW AND COMPETING RESEARCH PROJECT GRANTS EACH YEAR SINCE 1980, AND IN 1983 THE TOTAL WAS ALMOST 5,300, IT IS DIFFICULT TO CONTEND THAT MAINTENANCE OF THIS NUMBER HAS PRODUCED STABILITY IN THE FACE OF REPEATED AND UNPREDICTABLE REDUCTIONS IN DIRECT COSTS OF EVERY RESEARCH SUPPORT MECHANISM, INCLUDING PROJECT GRANTS, TRAINING AND CAREER AWARDS, AND RESEARCH CENTERS.

ONE COMPONENT OF THE LONG-RANGE STABILIZATION EFFORT--5,000 NEW AND COMPETING GRANTS--IS EASY TO DESCRIBE AND, AS THINGS HAVE TURNED OUT, IS ACHIEVABLE. IT IS NOT SURPRISING THAT THIS PARTIAL EXPRESSION OF A BROADER OBJECTIVE HAS BECOME ITS SURROGATE AND THE FOCUS OF ATTENTION FROM ALL CONCERNED.

NUMEROUS PROPOSALS HAVE BEEN MADE RECENTLY TO "STRETCH" THE RESEARCH DOLLAR BY LIMITING OR REDUCING THE AMOUNTS PAID ON INDIVIDUAL GRANTS IN ORDER TO FREE FUNDS TO SUPPORT ADDITIONAL AWARDS.

THESE PROPOSALS HAVE BEEN CONSIDERED BY THE NIH AND HAVE BEEN FOUND TO BE LACKING IN MANY RESPECTS, NOT THE LEAST OF WHICH IS THE IMPLICATION THAT RESEARCH AWARDS REPRESENT A FULL EMPLOYMENT PROGRAM FOR SCIENTISTS.

HOWEVER, IN FY 1982, THE NIH INSTITUTED A FORMAL POLICY OF AWARDING GRANTS AT AMOUNTS LESS THAN THOSE RECOMMENDED BY THE PEER REVIEW GROUPS AS A WAY OF MAXIMIZING THE NUMBER OF GRANTS THAT COULD BE SUPPORTED WITHIN A GIVEN BUDGET LEVEL.

ALTHOUGH AS DEMONSTRATED BY THE 1982 AND 1983 EXPERIENCE, THIS POLICY HAS PROVIDED SHORT-TERM RELIEF FROM BUDGET STRINGENCIES, IT HOLDS LITTLE PROMISE OF CONTRIBUTING TO LONG-TERM SOLUTIONS. JUST AS THERE ARE LIMITS TO THE AMOUNTS OF RESOURCES THAT CAN BE SHIFTED FROM OTHER PROGRAM MECHANISMS TO SUPPORT THE FUNDING OF RESEARCH PROJECT GRANTS, SO ARE THERE LIMITS TO THE REDUCTIONS THAT CAN BE MADE IN FUNDS AWARDED TO SUPPORT OF AN INDIVIDUAL RESEARCH PROJECT GRANT WITHOUT DEFEATING THE PURPOSES FOR WHICH THOSE FUNDS WERE AWARDED.

DESPITE THE UNTOWARD SIDE EFFECTS OF THE RECENT PARTIAL IMPLEMENTATION OF A STABILIZATION POLICY, THE NIH HAS NO DESIRE TO ABANDON THE CONCEPT--AND WE RECOGNIZE THE POSITIVE EFFECT OF EVEN AN INCOMPLETE APPLICATION OF THIS LONG-RANGE PLAN DURING A TIME OF FISCAL STRINGENCY. IT IS OUR CONVICTION THAT THE IMPORTANT NEEDS ADDRESSED BY THE ORIGINAL STABILIZATION STRATEGY REMAIN AND THAT THE ESSENTIAL COMPONENTS OF THE STRATEGY CONTINUE TO BE VITAL AS MEANS FOR ADDRESSING THOSE NEEDS.

STATED IN THE SIMPLEST POSSIBLE TERMS, WE NEED TO ASSURE ADEQUATE LEVELS OF SUPPORT FOR THE ENTIRE RESEARCH ENTERPRISE IF WE ARE TO PRESERVE THE MOMENTUM OF DISCOVERY. WE BELIEVE THAT THE OPTIMAL LEVEL FOR PROGRESS IS TO BE ABLE TO AWARD 45 TO 50 PERCENT OF APPROVED APPLICATIONS FOR RESEARCH SUPPORT. IN THE CONTEXT OF THE FEDERAL BUDGET, THE SUMS NEEDED ARE NOT LARGE. LAST DECEMBER I EXPRESSED TO THE DIRECTOR'S ADVISORY COMMITTEE MY BELIEF THAT TO ACHIEVE SUCH A GOAL, WE WOULD NEED AN ADDITIONAL THREE TO FOUR HUNDRED MILLION DOLLARS PER YEAR. IT IS ENCOURAGING THAT THE INCREASE FOR 1984 FALLS WELL WITHIN THAT PROJECTION.

BUT A PROJECTION BASED ON A 50 PERCENT AWARD RATE, FULL FUNDING OF GRANTS, AND MAINTENANCE OF BALANCE AMONG THE ESSENTIAL MECHANISMS FOR RESEARCH SUPPORT WOULD REACH AN ANNUAL TOTAL OF NEARLY $10 BILLION BY 1990 EVEN IF A MODEST RATE OF INFLATION IS ASSUMED.

IN SPEAKING OF THE ESSENTIAL MECHANISMS FOR RESEARCH SUPPORT, I WOULD INCLUDE AT THE MINIMUM ADEQUATE FUNDING FOR CENTERS, FOR CONTRACTS, FOR INTRAMURAL RESEARCH AND FOR TRAINING, AS WELL AS FOR RESEARCH GRANTS [← ? How see p']

[Grants]

ANOTHER MATTER REQUIRING ATTENTION IS THE NEED TO REPLACE OR PURCHASE THE INCREASINGLY SOPHISTICATED INSTRUMENTS REQUIRED FOR TODAY'S RESEARCH. IT IS ESTIMATED THAT 20 MILLION DOLLARS A YEAR FOR FIVE YEARS IS NEEDED FOR THE ACQUISITION OF LARGE-SCALE SHARED INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE THROUGH RESEARCH GRANTS OF SMALLER INSTRUMENTS. THE NIH HAS RECENTLY JOINED AN ONGOING STUDY BY THE NATIONAL SCIENCE FOUNDATION FOR THE PURPOSE OF SECURING A VALID CURRENT ASSESSMENT OF NATIONAL NEED.

FINALLY, EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND MORE RECENTLY BY THE NATIONAL EYE INSTITUTE, NIH STOPPED SUPPORTING FACILITIES AFTER 1969.

AS A CONSEQUENCE, MANY OF THE FACILITIES BENEFITING FROM THE MAJOR NIH CONSTRUCTION EFFORT--THE HEALTH RESEARCH FACILITIES PROGRAM--ARE MORE THAN 20 YEARS OLD, OR RAPIDLY APPROACHING THAT MARK.

RATHER THAN CALLING FOR ANY NEW MAJOR EXPANSION, THE REALISTIC AIM OF ANY NEW FEDERAL CONSTRUCTION PROGRAM SHOULD PROBABLY BE LESS AMBITIOUS. IT SHOULD, HOWEVER, INCLUDE NEW CONSTRUCTION TO REPLACE OUTMODED FACILITIES, TO RELIEVE OVERCROWDING, AND TO ACCOMMODATE CHANGING RESEARCH REQUIREMENTS, INCLUDING FACILITIES FOR DEALING WITH TOXIC WASTES, FACILITIES TO LABORATORY ANIMALS, AND FOR MAJOR RENOVATION AND REPAIR OF INFERIOR FACILITIES. THERE IS A DEARTH OF GOOD INFORMATION ON CONSTRUCTION NEEDS, AND A CURRENT STUDY SIMILAR TO THAT BEING CONDUCTED ON INSTRUMENTATION DEFICITS IS SERIOUSLY NEEDED.

IT IS CLEAR THAT FOR A CONSTRUCTION PROGRAM TO MAKE ANY DIFFERENCE IN ADDRESSING THE NEEDS, THE MONIES APPROPRIATED WOULD HAVE TO BE SUBSTANTIAL. PAST APPROACHES WHICH HAVE LIMITED THE TOTAL FEDERAL CONSTRUCTION CONTRIBUTION TO UP TO SOME FIXED PERCENTAGE OF TOTAL COSTS MAY BE A REASONABLE CONDITION TO IMPOSE ON ANY NEW AUTHORITY DEVELOPED. IT IS ENCOURAGING TO NOTE THAT THE CONGRESS HAS RECOGNIZED THAT UNIVERSITIES AND OTHER

INSTITUTIONS OF HIGHER LEARNING ARE REACHING A POINT WHERE THEY WILL NOT BE ABLE TO FULLY PARTICIPATE IN OUR COOPERATIVE RESEARCH ENDEAVOR ~~WITH THEM.~~ WITHOUT ASSISTANCE

AS IMPORTANT AS BUILDINGS AND ADEQUATE INSTRUMENTATION MAY BE, THERE IS ANOTHER CONSIDERATION OF EVEN GREATER MOMENT. THIS SUBJECT IS NECESSARILY AT THE HEART OF ANY DISCUSSION ABOUT PRESERVING THE MOMENTUM OF DISCOVERY OR OF PRESERVING THE BIOMEDICAL RESEARCH ENTERPRISE ITSELF. THAT SUBJECT IS RESEARCH TRAINING.

IN OUR VIEW, THE TRAINING AND RESEARCH PROGRAMS ARE SO CLOSELY INTERWOVEN AS TO BE PRACTICALLY INDIVISIBLE.

THE INTENSE COMPETITION FOR RESEARCH SUPPORT HAS INCREASINGLY TAKEN ITS TOLL OF THE AMATEUR OR UNDERTRAINED INVESTIGATOR. THE PROFESSIONALIZATION OF RESEARCH ACTIVITY HAS PROGRESSIVELY SELECTED AGAINST THE M.D. SCIENTIST WHO 15 YEARS AGO HAD A MUCH BETTER PROSPECT OF SUCCESS IN RESEARCH APPLICATIONS THAN THE PH.D. APPLICANT.

CONCURRENTLY, THERE HAS BEEN A DECREASE IN THE NUMBER OF PHYSICIANS WHO ARE SEEKING RESEARCH TRAINING.

THE APPLICATION OF SCIENTIFIC ADVANCES TO MAINTAIN GOOD HEALTH AND TO PREVENT AND TREAT DISEASE IS ULTIMATELY THE RESPONSIBILITY OF THE PHYSICIAN. THE TRAINED CLINICAL INVESTIGATOR IS THE CRITICAL LINK BETWEEN THE LABORATORY AND THE HEALTH CARE PROVIDER. IN THE FACE OF THE EXPLOSIVE GROWTH OF BASIC KNOWLEDGE IN THE BIOMEDICAL SCIENCES WHICH HAS OPENED UP VAST OPPORTUNITIES FOR CLINICAL RESEARCH, THE SHORTFALL IN TRAINING OF CLINICAL INVESTIGATORS ASSUMES ADDITIONAL SIGNIFICANCE.

DESPITE THESE NEGATIVE FACTORS AND PARTLY TO COUNTER THEM, THE NIH HAS DEVELOPED SEVERAL PROGRAMS IN ADDITION TO ITS REGULAR RESEARCH TRAINING GRANTS THAT ARE DESIGNED TO ACQUAINT THE PHYSICIAN IN TRAINING WITH THE EXCITEMENT AND POSSIBILITIES OF BIOMEDICAL RESEARCH.

AT THE PRESENT TIME, THE STIPENDS AVAILABLE FOR SUPPORT OF NATIONAL RESEARCH SERVICE AWARD TRAINEES ARE PALTRY, WELL BELOW THOSE AVAILABLE IN OTHER FEDERAL RESEARCH TRAINING PROGRAMS. PREDOCTORAL STIPENDS SHOULD BE RAISED TO THE $8,100 THAT IS OFFERED BY THE NATIONAL SCIENCE FOUNDATION. AN ESTIMATED SUPPLEMENT OF SOME $34 MILLION WOULD BE REQUIRED TO ACHIEVE PARITY UNDER THE NRSA PROGRAM. OUR NEW TRAINING PROGRAMS FOR EXCEPTIONAL

POSTDOCTORAL FELLOWS WOULD REQUIRE MORE THAN $10 MILLION TO BRING THEIR STIPEND LEVELS IN LINE WITH OTHER INDIVIDUALS OF EQUIVALENT TRAINING AND EXPERIENCE.

ADDITIONAL TRAINING SLOTS SHOULD BE MADE AVAILABLE FOR THE NRSA PROGRAM TO BRING IT TO THE LEVEL RECOMMENDED BY THE NATIONAL ACADEMY OF SCIENCES. OVER A TWO-YEAR PERIOD, TRAINING POSITIONS SHOULD BE INCREASED BY ABOUT 1,500. SIMILAR INCREASES ARE NEEDED IN THE CAREER DEVELOPMENT PROGRAM AT A RATE OF 200 ADDED AWARDS A YEAR FOR THREE YEARS. THE LATTER INCREASES, PLUS THE INCREASE IN NUMBERS OF NRSA TRAINEES, WOULD REQUIRE AN ADDITION OF SOME $40 MILLION PER YEAR.

EARLIER I SPOKE OF SOME OF THE EXTERIOR CHANGES THAT HAVE OCCURRED AFFECTING THE LONG-STANDING FEDERAL-ACADEMIC PARTNERSHIP. RECENTLY WE HAVE SEEN THE BEGINNINGS OF DEVELOPMENT OF A THREE-WAY PARTNERSHIP INVOLVING INDUSTRY AS A PARTICIPANT.

THERE HAVE BEEN SUGGESTIONS THAT THE NIH TAKE SOME KIND OF ACTIVE PART IN THE INSTITUTION OF THESE NEW RELATIONSHIPS. WE HAVE NOT DONE SO. WE BELIEVE IT PREFERABLE THAT THE NEW FORMS OF JOINT ENDEAVOR CONTINUE TO EVOLVE AS THEY HAVE BEEN WITH GOVERNMENT PLAYING A FACILITATIVE ROLE.

NOTWITHSTANDING THE FACT THAT THE AREAS OF COLLABORATION BETWEEN THE UNIVERSITIES AND INDUSTRY HAVE BROADENED SIGNIFICANTLY AND PROMISE TO CONTINUE IN THAT EXPANSION, I BELIEVE IT SAFE TO PREDICT THAT THE GOVERNMENT WILL CONTINUE AS THE PRINCIPAL SOURCE OF FUNDING FOR BASIC RESEARCH.

AT THE SAME TIME, AND WITHIN THE BIOMEDICAL SCIENTIFIC ENTERPRISE ITSELF, THERE HAS BEEN A GRADUAL CHANGE HAVING PROFOUND IMPLICATIONS. NOBEL LAUREATE ARTHUR KORNBERG RECENTLY CALLED ATTENTION TO THE "CONFLUENCE OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SUBJECTS INTO A SINGLE UNIFIED DISCIPLINE." HE OBSERVED THAT "ANATOMY, PHYSIOLOGY, BIOCHEMISTRY, MICROBIOLOGY, IMMUNOLOGY AND GENETICS HAVE NOW BEEN MERGED AND ARE EXPRESSED IN A COMMON LANGUAGE OF CHEMISTRY."[3]

IT IS IRONIC THAT IN THE PRESENCE OF THIS CONFLUENCE OF THE SCIENTIFIC DISCIPLINES, THERE ARE INCREASING PRESSURES ON THE NIH FOR FRAGMENTATION THROUGH THE CREATION

OF NEW ORGANIZATIONAL ENTITIES EACH HAVING A RELATIVELY NARROW FOCUS ON A PARTICULAR SET OF HEALTH PROBLEMS.

SUCH MOVEMENTS GAIN MUCH OF THEIR STRENGTH FROM, AND INDEED ARE AN EXPRESSION OF, THE PUBLIC CONFIDENCE IN THE POWER OF RESEARCH. THE MOVEMENTS ARE ALSO AN UNDERSTANDABLE REACTION BY SEGMENTS OF THE BIOMEDICAL COMMUNITY TO THE FUNDING CRUNCH AND REPRESENT AN EFFORT TO ESTABLISH ALTERED RESEARCH PRIORITIES THROUGH CONGRESSIONAL ACTION.

THE NIH AND THE DEPARTMENT OF HEALTH AND HUMAN SERVICES HAVE OPPOSED LEGISLATION FOR THE CREATION OF NEW INSTITUTES AND FOR THE ESTABLISHMENT IN STATUTE OF FAVORED STATUS FOR SPECIFIC RESEARCH PROGRAMS. OUR OPPOSITION TO THESE PROPOSALS IS BASED NOT ONLY ON THEIR ADVERSE EFFECTS ON ADMINISTRATIVE COSTS AND FLEXIBILITY, BUT ALSO BECAUSE THE COMPARTMENTALIZATION THEY ESTABLISH IS COUNTER TO THE DIRECTION IN WHICH SCIENCE IS MOVING. AT A TIME WHEN WE <u>CAN</u> CONFIDENTLY PREDICT UNUSUALLY RAPID MOVEMENT IN SCIENCE, AND WE <u>CANNOT</u> PREDICT JUST WHERE THAT PROGRESS WILL OCCUR, WE NEED THE MAXIMUM FLEXIBILITY FOR MARSHALING FINITE RESOURCES FOR SUPPORT OF SCIENCE. ORGANIZATIONAL STRUCTURES HAVE A DIRECT INFLUENCE ON FUNDING PRIORITIES. EVEN THOUGH SUCH DETAILED LEGISLATIVE PRESCRIPTIONS MAY BE

PROPOSED WITH THE INTENT OF PRESERVING THE SCIENTIFIC ENTERPRISE, THEIR EFFECT CAN TEND TOWARD ANOTHER KIND OF PRESERVATION--FREEZING THE ENTERPRISE IN STATUS QUO.

IN SAYING THIS, HOWEVER, I AM AWARE THAT ADAMANT REFUSAL ON THE PART OF THE SCIENTIFIC AND ACADEMIC COMMUNITY TO CONSIDER CHANGE IS SHORTSIGHTED. SUCH A POSTURE WOULD IGNORE THE HISTORY OF THE DEVELOPMENT OF THE NIH--INSTITUTE BY INSTITUTE AND MOST OF THEM DISEASE-ORIENTED. IT WAS FROM SUCH SPECIFICITY THAT PUBLIC INTEREST AND VIGOROUS SUPPORT WAS DRAWN.

THE PRESERVATION AND RAPID FLOWERING OF THE BIOMEDICAL RESEARCH ENTERPRISE WAS NOT ACCOMPLISHED BY MAKING THE AGENCY A PRESERVE FOR SCIENTISTS. IT IS INSTRUCTIVE TO NOTE THAT THE NAME IS THE NATIONAL INSTITUTES OF HEALTH AND NOT THE NATIONAL INSTITUTES OF RESEARCH.

LAST JUNE, WE ASKED THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES TO MAKE AN OBJECTIVE STUDY OF THE ORGANIZATIONAL STRUCTURE OF THE NIH AND, CONSIDERING SCIENTIFIC DEVELOPMENTS AND ECONOMIC CONDITIONS, TO RECOMMEND THE ESTABLISHMENT OF STANDARDS FOR DETERMINING THE NEED FOR ANY SUBSTANTIAL CHANGE IN THE ORGANIZATIONAL STRUCTURE OF THE AGENCY. WE EXPECT THE STUDY TO BE COMPLETED AND TO HAVE A REPORT FROM THE IOM IN NOVEMBER 1984.

IN THAT CONNECTION, PERMIT ME TO LAY TO REST ONE BIT OF FALSE SPECULATION THAT HAS CIRCULATED IN SOME QUARTERS OF THE SCIENTIFIC COMMUNITY; NAMELY, THAT NIH'S HIDDEN AGENDA IN SPONSORING THE IOM STUDY IS TO DO AWAY WITH CATEGORICAL INSTITUTES. IF YOU WILL PARDON THE EXPRESSION, I CAN CATEGORICALLY SAY THAT WE DID NOT AND DO NOT HAVE SUCH AN INTENTION.

MOST OF YOU WILL REMEMBER THE REPORT BY LOWELL T. COGGESHALL, ISSUED BY THE AAMC IN 1965, TITLED "PLANNING FOR MEDICAL PROGRESS THROUGH EDUCATION." IN THE REPORT WAS AN OBSERVATION THAT FITS EXACTLY THE CONTEXT OF MY REMARKS AND, IN A SENTENCE, ~~ENCAPSULES~~ CAPTURES THE IDEAS I HAVE ENDEAVORED TO PRESENT. IN DR. COGGESHALL'S WORDS--AS VALID NOW AS WHEN THEY WERE WRITTEN--"THE IMPORTANT QUESTION FOR THE FUTURE IS WHETHER THE PRESENT SYSTEM IS SUFFICIENTLY FLEXIBLE AND IMAGINATIVE TO KEEP PACE WITH THE CONTEMPORARY REVOLUTION IN MEDICAL SCIENCES AND THE CHANGING EXPECTATIONS OF THE AMERICAN PEOPLE."

INTRODUCTORY REMARKS*

by

James B. Wyngaarden, M.D.**

There's a saying that success has many fathers but failure is an orphan. Bob, you have many fathers in this room today. People have come to honor you as the winner of the Lita Annenberg Hazen Award for 1983. Those who have been associated with you in whatever capacity are proud of your accomplishments and your selection. They share vicariously in your award and, as you have already discovered, may be inclined to take some of the credit for it. In my case, having been Chairman of the Department of Medicine at Duke for ten of your most productive years, I am sometimes tempted to behave as a European Geheimrat and take full credit for all of your discoveries.

I first met Bob Lefkowitz when Andy Wallace, then Chief of Cardiology in the Department of Medicine at Duke, invited Bob and his wife, Arna, to visit Duke in late 1972 or early 1973. Six of us went out to dinner at the Frog and Nightgown in Raleigh. I was immediately impressed with Bob's enthusiasm, energy, and good sense of humor. I already knew that he was bright from things that Andy had told me. During the course of the evening, probably the second course, as I chatted with Arna and learned they had

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**Director, National Institutes of Health, Bethesda, Maryland.

four children and planned at least one more, and that she was an artist, I realized just how bright Bob was. We offered Bob an associate professorship at Duke, which he accepted. Bob was 30 at the time.

The coin of the realm in academic medicine is space. We had just completed a magnificent research building, and I was able to show Bob gleaming new laboratories. I think these had something to do with Bob's decision to come to Duke. I've often thought how fortunate Duke was to have attractive new space at just that moment, and how problematic recruitment might have been had we approached Bob one year earlier or one year later. As you know, space abhors a vacuum and timing in such connections is all important.

Bob proved to be an ideal faculty member from my point of view because he never cost me anything. He raised his own research and salary support. He also never came to ask for more money. When the Lefkowitz' had their fifth child or Arna needed a new set of paint brushes, Bob simply went out and won another prize. He had already won the Roche and Janeway prizes as a medical student at Columbia. In 1973 he became an established investigator of the American Heart Institute, and in 1976 a Howard Hughes Medical Institute investigator. In 1978 he won the Young Scientist Award of the Passano Foundation, and also in 1978 the John Jacob Abel Award in Pharmacology. In 1979 he won the Young Investigator Award of the American College of Clinical Pharmacology, and also in 1979 the George W. Thorn Award for Scientific Excellence of the Howard Hughes Medical Institute. 1982 was

another big year when he won the Ernst Oppenheimer Memorial Award of the Endocrine Society, the Gordon Wilson Medal of the American Clinical and Climatological Association, and was named a James B. Duke Professor at Duke University. He was 39 at the time, the youngest ever to be elevated to that prestigious professorship at Duke.

Bob's research has involved catecholamine and insulin receptors. Before coming to Duke he worked on ACTH receptors in the laboratory of Jesse Roth at the NIH. Jesse, as you know, was the first recipient of the Lita Annenberg Hazen Award. Still earlier, I am told that Bob was a wide receptor on his Little League football team.

I would like to highlight several special aspects of Bob's research career. The first relates to the profound importance of his findings with adrenergic receptors for receptor research generally. Few areas of biomedical research have so captured the imagination of investigators over the past decade as that relating to receptors, and few investigators have had as major an impact on this field as Bob. The conceptual, technical, and analytical approaches pioneered in his laboratory have served as models which have been emulated by workers studying receptors for varied types of hormones, drugs, and neurotransmitters. Thus, the importance of his work far transcends the area of adrenergic receptors and catecholamine action.

As an example, one might cite his discovery of the basic mechanisms by which hormones and drugs stimulate their effectors, and in turn the mechanisms by which the receptors become

desensitized to further stimulation. These contributions have involved the elucidation of some of the most basic and general mechanisms operative in human biology. Moreover, the work on desensitization has far-reaching, general implications for drug and hormone therapy. Since tachyphylaxis develops to almost all types of agonist drugs, hormones, and neurotransmitters, understanding its basic mechanisms now permits a rational approach to the development of strategies for circumventing these processes and prolonging and augmenting the actions of diverse therapeutic agents. Bob's work in providing molecular explanations for the altered hormonal (catecholamine) sensitivity in situations as varied as thyrotoxicosis, the propranolol withdrawal syndrome, glucocorticoid therapy and many others is a classic example of the physician-scientist translating the most fundamental scientific discoveries into the realm of clinical investigations.

Bob's career continues to integrate the roles of basic scientist, educator, clinical researcher, and physician. An effective and charismatic teacher, he has been an inspirational mentor to both basic and clinical young investigators. Bob catalyzed the receptor age in the Department of Medicine at Duke, not only in the Cardiovascular Division but also in Endocrinology, Immunology, Neurosciences, and Allergy. Several of his collaborators are here today to join in paying tribute to Dr. Lefkowitz, and thus to express their gratitude to him for his generous sharing of time and expertise in catalyzing their entry into new approaches to their research. In addition to Bob's prodigious research accomplishments, he has authored or coauthored two books

on receptors, a major biochemistry textbook, and has begun to assume duties as consulting editor for the Cecil Textbook of Medicine. He is equally at home in the worlds of biochemistry and medicine, and his research career mirrors this. I congratulate Dr. Lefkowitz, the 1983 exemplar of the cherished ideals of the Lita Annenberg Hazen Award.

SCIENTIFIC LEADERSHIP AND CREATIVITY*

BY

JAMES B. WYNGAARDEN, M.D.**

I AM DELIGHTED TO PARTICIPATE IN THIS PROGRAM HONORING BILL ANLYAN, MY COLLEAGUE AT DUKE FOR 25 YEARS AND VICE PRESIDENT FOR HEALTH AFFAIRS DURING ALL OF MY 15 YEARS AS A DEPARTMENTAL CHAIRMAN. THE TITLE OF MY ADDRESS, "SCIENTIFIC LEADERSHIP AND CREATIVITY," WAS SUGGESTED TO ME BY ANDY WALLACE WHEN HE CALLED TO INVITE ME TO SPEAK. AFTER CHECKING MY CALENDAR I IMMEDIATELY ACCEPTED BOTH BECAUSE OF MY GREAT AFFECTION FOR DUKE AND BILL ANLYAN, AND BECAUSE AS DIRECTOR OF NIH I TRAVEL AS MUCH AS I POSSIBLY CAN -- I HAVE LEARNED THAT IT IS HARDER TO HIT A MOVING TARGET, SO TRAVEL CONTRIBUTES TO SURVIVAL IN WASHINGTON. I LEARNED QUITE A LOT ABOUT TRAVEL FROM WATCHING MY COLLEAGUES AT DUKE FOR 25 YEARS. NONE HAVE TRAVELED MORE WIDELY THAN BILL ANLYAN AND DAVE SABISTON. I RECALL HOW IMPRESSED I WAS WITH BOTH OF THEM WHEN THEY FLEW TO KENNEDY AIRPORT TO DISCUSS MY RETURNING TO DUKE FROM PENNSYLVANIA IN EARLY 1967. EITHER

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* PRESENTED AT THE ANLYAN SYMPOSIUM ON NOVEMBER 11, 1983, AT DUKE UNIVERSITY, DURHAM, NORTH CAROLINA.

** DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.

WILL FLY 500 MILES OR 5000 MILES FOR DUKE ANYTIME. IN FACT, IF I EVER RUN INTO EITHER ONE AGAIN, I AM SURE I WILL STILL RECOGNIZE HIM. NOW THAT I AM HERE, I FEEL A BIT PRESUMPTIOUS TALKING ABOUT LEADERSHIP TO A DUKE AUDIENCE WHEN YOU HAVE SUCH AN OUTSTANDING EXAMPLE IN THE PERSON OF BILL ANLYAN. THE CURRENT ISSUE OF DUKE UNIVERSITY MEDICAL CENTER PERSPECTIVES HAS AN ARTICLE ABOUT BILL ENTITLED "TO FIND THE RIGHT PEOPLE." THAT IS AN ANLYAN AXIOM AND SURELY THE FIRST PRINCIPLE OF LEADERSHIP. THE SECOND MIGHT BE, "TO PROVIDE OPPORTUNITY FOR THEM TO GROW, AND TO EXPRESS THEIR TALENT." I KNOW OF NO INSTITUTION SUPERIOR TO DUKE IN THIS RESPECT. OPPORTUNITY REQUIRES RESOURCES AND DUKE HAS ALWAYS MANAGED SOMEHOW TO FIND THOSE IN REASONABLE MEASURE. BUT OPPORTUNITY ALSO REQUIRES FREEDOM, FREEDOM FROM TOO MANY DISTRACTING DEMANDS AND FREEDOM TO PURSUE ONE'S OWN IDEAS, ONE'S INTELLECTUAL CURIOSITY, ONE'S CREATIVITY--WITHOUT INTERFERENCE, WITHOUT DIRECTION OF ONE'S INTELLECTUAL LIFE BY THE MANAGERS OF THE ENTERPRISE. MANAGERS ARE NECESSARY TO PROVIDE THE RESOURCES, TO INSURE SOLVENCY, TO GET THE NECESSARY JOBS DONE -- BUT NOT TO PROVIDE CREATIVE IDEAS, AT LEAST NOT IF YOUR GOAL IS TO PRODUCE CREATIVE PEOPLE. AND THAT IS THE PARADOX: CREATIVE LEADERSHIP CONSISTS OF

CONSTRUCTING AN ENVIRONMENT OR A SYSTEM IN WHICH OTHERS CAN BE CREATIVE. DUKE IS A SPLENDID EXAMPLE OF ALL OF THESE PRINCIPLES, AND MY EXPERIENCES AT DUKE ARE SERVING ME WELL IN MY PRESENT ROLE AT THE NIH.

THE FUNDAMENTAL MISSION OF NIH IS TO DISCOVER NEW BIOMEDICAL KNOWLEDGE OF BENEFIT TO THE HEALTH AND WELL-BEING OF THE AMERICAN PEOPLE. TO ACHIEVE THAT OBJECTIVE IT IS NECESSARY TO FIND THE RIGHT PEOPLE. I WAS FORTUNATE IN HAVING 11 VACANCIES AMONG THE TOP 18 POSITIONS ON ARRIVAL AT THE NIH OR SHORTLY THEREAFTER. TEN OF THOSE 11 ARE NOW FILLED WITH EXCELLENT PEOPLE. THE MANAGEMENT LEVEL IS ESSENTIALLY COMPLETE. BUT THE DISCOVERIES THAT HAVE LED TO SUCH SPECTACULAR PROGRESS IN MEDICINE IN RECENT DECADES AND THAT CREATE SUCH HIGH HOPES FOR CONTINUED PROGRESS TOWARD THE CONQUEST OF THE MAJOR DISEASES THAT PLAGUE MANKIND ARE MADE NOT BY DIRECTORS, BUT BY SCIENTISTS PURSUING SOLUTIONS TO PUZZLES IN THE LABORATORIES THROUGHOUT THIS COUNTRY. THAT IS WHY IN OUR PROGRAMS, IN OUR BUDGET CONSTRUCTIONS, AND IN OUR TESTIMONIES TO THE CONGRESS WE PLACE SUCH EMPHASIS UPON THE INVESTIGATOR-INITIATED RESEARCH PROJECT GRANT TO GENERATE CREATIVE IDEAS, AND UPON THE PEER REVIEW SYSTEM TO SELECT OUT THOSE PROPOSALS THAT APPEAR TO HAVE THE

GREATEST SCIENTIFIC MERIT, THE GREATEST POTENTIALITY FOR CONTRIBUTING IMPORTANT NEW KNOWLEDGE. THIS IS ANOTHER EXAMPLE OF FINDING THE RIGHT PEOPLE FOR THE RIGHT JOBS.

THE COURSE OF NIH AND OF BIOMEDICAL RESEARCH IN THIS COUNTRY WAS DEEPLY INFLUENCED NEARLY 10 YEARS AGO BY AN INSIGHTFUL TREATISE ENTITLED, "SCIENCE -- THE ENDLESS FRONTIER," PREPARED IN 1945 BY THE PRESIDENT'S SCIENCE ADVISOR VANNEVAR BUSH. THIS DOCUMENT, WHICH LAID OUT THE MAJOR PRINCIPLES STILL HELD BY NIH, SET THE TRACK FOR LEGISLATIVE ACTION TO FOLLOW. BUSH SAW THAT FOSTERING CREATIVITY IN SCIENCE WAS THE FUNDAMENTAL INGREDIENT OF CONTINUED PROGRESS. IT WAS HE WHO FIRMLY SET THE CENTER OF BIOMEDICAL RESEARCH IN THE ACADEMIC INSTITUTIONS RATHER THAN PRIMARILY IN FREE-STANDING RESEARCH INSTITUTES. PERMIT ME TO READ A FEW SENTENCES FROM HIS REPORT: "THE PUBLICLY AND PRIVATELY SUPPORTED COLLEGES, UNIVERSITIES, AND RESEARCH INSTITUTES ARE THE CENTERS OF BASIC RESEARCH. THEY ARE THE WELLSPRINGS OF KNOWLEDGE AND UNDERSTANDING. AS LONG AS THEY ARE VIGOROUS AND HEALTHY, AND THEIR SCIENTISTS ARE FREE TO PURSUE THE TRUTH WHEREEVER IT MAY LEAD, THERE WILL BE A FLOW OF NEW SCIENTIFIC KNOWLEDGE." THUS, RESPONSIBILITY OF THE FEDERAL GOVERNMENT WAS TO <u>HELP</u> THE ACADEMIC INSTITUTIONS

FOSTER A CREATIVE ENVIRONMENT AND TO AID THEM IN MAINTAINING THEIR VIGOR AND HEALTH.

In 1955, when Dr. James A. Shannon became Director, the time was ripe for rapid expansion of the NIH and its programs. The budget of the agency was then $82 million, and when he retired 13 years later the budget had topped $1 billion. During his tenure, NIH became virtually complete, only three more institutes being added later. The results of his creative leadership have served as well. Dr. Shannon insisted that the Congressional mandates to conduct research in Cancer, Heart disease and Arthritis, for example, be interpreted broadly. He realized that the science base was not sufficient to permit a frontal assault on the diseases themselves. He set about to build the research capability of this country in part through the intramural program in Bethesda, but chiefly through a great expansion of the system of grants-in-aid to the academic institutions. Corollary objectives included the strengthening of the institutions in which biomedical research would be done, and the development of training mechanisms that would ensure a continuing supply of competent scientists drawn from the best and the brightest young minds in the universities.

TOGETHER WITH HILL-BURTON MONEY FOR CLINICAL FACILITIES, NIH CONSTRUCTION FUNDS FOR RESEARCH FACILITIES MODIFIED THE TOPOGRAPHY OF THE ACADEMIC MEDICAL CENTER AND INDIRECTLY CHANGED AND STRENGTHENED MEDICAL EDUCATION.

THE PERIOD OF LEADERSHIP HELD BY DR. DONALD S. FREDRICKSON, FROM 1975-1981, PRESENTED A NEW CHALLENGE TO CREATIVE LEADERSHIP: THE BIOLOGICAL REVOLUTION WAS AT FULL FORCE AND SCIENTIFIC OPPORTUNITY ABOUNDED. THE APPROPRIATION FOR NIH CONTINUED TO GROW AND EXCEEDED $3 BILLION FOR THE FIRST TIME. BUT INFLATION WAS TAKING ITS TOLL AND THE GROWTH IN SUPPORT WAS MORE APPARENT THAN REAL. THE TIME HAD COME FOR A REASSESSMENT OF PROGRAMS AND POLICIES IN ORDER TO MAINTAIN THE MOMENTUM OF SCIENTIFIC INQUIRY IN THE FACE OF A DECLINE IN PURCHASING POWER. THE ANSWER WAS A STRATEGY FOR STABILIZATION OF THE SCIENCE BASE. A MAJOR FOCUS OF THIS POLICY WAS TO MAINTAIN A STEADY AND PREDICTABLE LEVEL OF SUPPORT FOR INVESTIGATOR-INITIATED RESEARCH PROJECTS AND THE TRAINING OF NEW INVESTIGATORS WHILE CONTINUING TO CARRY OUT OTHER IMPORTANT RESPONSIBILTIES. AS A RESULT OF THE STABILIZATION POLICY, FUNDS HAVE BEEN SHIFTED FROM OTHER MECHANISMS INTO RESEARCH PROJECT GRANTS WHICH NOW COMPRISE ABOUT 83% OF OUR

EXTRAMURAL BUDGET. HOW WELL HAS NIH SUCCEEDED IN PROVIDING SCIENTIFIC LEADERSHIP AND IN FOSTERING CREATIVITY? LET ME QUOTE FROM DR. LEWIS THOMAS, THE POET LAUREATE OF AMERICAN MEDICINE AND THIS COUNTRY'S PREMIER BIOLOGY-WATCHER. IN A PREFACE TO A NEW BOOK RECOUNTING SOME OF THE ACHIEVEMENTS OF INTRAMURAL NIH, HE WRITES: "WE SEEM TO BE LIVING THROUGH A PERIOD (TRANSIENT, I HOPE) OF PUBLIC DISILLUSION AND DISCOURAGEMENT OVER GOVERNMENT AND ALL ITS WORKS. AT ALL LEVELS, BUREAUCRACY IN GENERAL IS MISTRUSTED, HERE AND ABROAD. THE WORD IS OUT THAT GOVERNMENT DOESN'T REALLY WORK, CAN'T GET THINGS RIGHT, WASTES PUBLIC MONEY, FUMBLES ALONG, STALLS, GETS IN THE WAY.

"AT SUCH A TIME, IT LIFTS THE HEART TO LOOK CLOSELY AT ONE INSTITUTION CREATED BY THE UNITED STATES GOVERNMENT WHICH HAS BEEN ACHIEVING, SINCE ITS OUTSET, ONE SPECTACULAR, STUNNING SUCCESS AFTER ANOTHER. THE NATIONAL INSTITUTES OF HEALTH IS NOT ONLY THE LARGEST INSTITUTION FOR BIOMEDICAL RESEARCH ON EARTH; IT IS ONE OF THIS NATION'S GREAT TREASURES. AS SOCIAL INVENTIONS FOR HUMAN BETTERMENT GO, THIS ONE IS A STANDING PROOF THAT, AT LEAST ONE IN A WHILE, GOVERNMENT POSSESSES THE CAPACITY TO DO SOMETHING UNIQUE, IMAGINATIVE, USEFUL, AND ALTOGETHER RIGHT."

THAT IS HIGH PRAISE, FROM AN OBJECTIVE IF PERHAPS NOT AN ENTIRELY NEUTRAL OBSERVER. BUT WE ARE NOT WITHOUT OUR PROBLEMS AND CHALLENGES FOR CREATIVE LEADERSHIP. LET ME BRIEFLY DISCUSS 4 TOPICS -- RESEARCH SUPPORT, RESEARCH TRAINING, INSTRUMENTATION, AND FACILITIES.

RESEARCH SUPPORT

NIH HAS HISTORICALLY SUPPORTED ABOUT 50 PERCENT OF GRANT APPLICATIONS APPROVED BY STUDY SECTIONS. IN THE LAST FEW YEARS WE WERE ABLE TO SUPPORT ONLY ABOUT 33 PERCENT OF SUCH GRANTS, ALTHOUGH IN FY '83, WHICH JUST ENDED ON SEPTEMBER 30, WE REACHED A LEVEL OF 39 PERCENT. EVEN TO SUPPORT THESE LEVELS REQUIRED CUTBACKS IN SUPPORT OF CENTERS, CONTRACTS, AND TRAINING. WE DO SUPPORT A LARGE NUMBER OF PROJECTS: ABOUT 16,500 P01'S AND R01'S IN 1983 COMPARED WITH 9000 IN 1973. BUT THE POOL OF TALENTED SCIENTISTS HAS GROWN FASTER THAN RESEARCH SUPPORT -- OUR BUDGET HAS BEEN VIRTUALLY LEVEL IN PURCHASING POWER FOR A DECADE -- AND COMPETITION FOR SUPPORT IS INTENSE, PARTICULARLY AMONG YOUNG SCIENTISTS WHO ARE THE HOPE OF THE FUTURE.

(GRIZZLY BEAR STORY)

NUMEROUS PROPOSALS HAVE BEEN MADE RECENTLY TO "STRETCH" THE RESEARCH DOLLAR BY LIMITING OR REDUCING THE AMOUNTS PAID ON INDIVIDUAL GRANTS IN ORDER TO FREE FUNDS TO SUPPORT ADDITIONAL AWARDS. THE EXTREME EXAMPLE OF THIS IS THE SLIDING SCALE PROPOSAL UNDER WHICH, IT IS SUGGESTED, ALL APPROVED APPLICATIONS SHOULD RECEIVE SOME FUNDING.

THESE PROPOSALS HAVE BEEN CONSIDERED BY THE NIH AND HAVE BEEN FOUND TO BE LACKING IN MANY RESPECTS, NOT THE LEAST OF WHICH IS THE IMPLICATION THAT RESEARCH AWARDS REPRESENT A FULL EMPLOYMENT PROGRAM FOR SCIENTISTS. THE PROPOSAL BRINGS TO MIND A STATEMENT IN TESTIMONY BY PHILIP HANDLER: "IN SCIENCE THE BEST IS VASTLY MORE IMPORTANT THAN THE NEXT BEST," OR JOHN GARDNER'S QUERY, "CAN WE BE EQUAL AND EXCELLENT, TOO?"

HOWEVER, IN FY 1982, THE NIH INSTITUTED A FORMAL POLICY OF AWARDING GRANTS AT AMOUNTS LESS THAN THOSE RECOMMENDED BY THE PEER REVIEW GROUPS AS A WAY OF MAXIMIZING THE NUMBER OF GRANTS THAT COULD BE SUPPORTED WITHIN A GIVEN BUDGET LEVEL.

ALTHOUGH AS DEMONSTRATED BY THE 1982 AND 1983 EXPERIENCE, THIS POLICY HAS PROVIDED SHORT-TERM RELIEF FROM BUDGET STRINGENCIES, IT HOLDS LITTLE PROMISE OF CONTRIBUTING

TO LONG-TERM SOLUTIONS. JUST AS THERE ARE LIMITS TO THE AMOUNTS OF RESOURCES THAT CAN BE SHIFTED FROM OTHER PROGRAM MECHANISMS TO SUPPORT THE FUNDING OF RESEARCH PROJECT GRANTS, SO ARE THERE LIMITS TO THE REDUCTIONS THAT CAN BE MADE IN FUNDS AWARDED TO SUPPORT OF AN INDIVIDUAL RESEARCH PROJECT GRANT WITHOUT DEFEATING THE PURPOSES FOR WHICH THOSE FUNDS WERE AWARDED.

DESPITE THE UNTOWARD SIDE EFFECTS OF THE RECENT PARTIAL IMPLEMENTATION OF A STABILIZATION POLICY, THE NIH HAS NO DESIRE TO ABANDON THE CONCEPT -- AND WE RECOGNIZE THE POSITIVE EFFECT OF EVEN AN INCOMPLETE APPLICATION OF THIS LONG-RANGE PLAN DURING A TIME OF FISCAL STRINGENCY. IT IS OUR CONVICTION THAT THE IMPORTANT NEEDS ADDRESSED BY THE ORIGINAL STABILIZATION STRATEGY REMAIN AND THAT THE ESSENTIAL COMPONENTS OF THE STRATEGY CONTINUE TO BE VITAL AS MEANS FOR ADDRESSING THOSE NEEDS.

STATED IN THE SIMPLEST POSSIBLE TERMS, WE NEED TO ASSURE ADEQUATE LEVELS OF SUPPORT FOR THE ENTIRE RESEARCH ENTERPRISE IF WE ARE TO PRESERVE THE MOMENTUM OF DISCOVERY. WE BELIEVE THAT THE OPTIMAL LEVEL FOR PROGRESS IS TO BE ABLE TO AWARD 45 TO 50 PERCENT OF APPROVED APPLICATIONS FOR

RESEARCH SUPPORT. IN THE CONTEXT OF THE FEDERAL BUDGET, THE SUMS NEEDED ARE NOT LARGE. LAST DECEMBER I EXPRESSED TO THE DIRECTOR'S ADVISORY COMMITTEE MY BELIEF THAT TO ACHIEVE SUCH A GOAL, WE WOULD NEED AN ADDITIONAL THREE TO FOUR MILLION DOLLARS PER YEAR. IT IS ENCOURAGING THAT THE INCREASE FOR 1984 FALLS WELL WITHIN THAT PROJECTION.

BUT A PROJECTION BASED ON A 50 PERCENT AWARD RATE, ESSENTIALLY FULL FUNDING OF GRANTS, AND MAINTENANCE OF BALANCE AMONG THE ESSENTIAL MECHANISMS FOR RESEARCH SUPPORT WOULD REQUIRE MUCH LARGER SUMS, PERHAPS A DOUBLING OF THE NIH BUDGET BY 1990 EVEN IF A MODEST RATE OF INFLATION IS ASSUMED.

IN SPEAKING OF THE ESSENTIAL MECHANISMS FOR RESEARCH SUPPORT, I WOULD INCLUDE AT THE MINIMUM ADEQUATE FUNDING FOR CENTERS, FOR CONTRACTS, FOR INTRAMURAL RESEARCH AND FOR TRAINING, AS WELL AS FOR RESEARCH GRANTS. FOR OBVIOUS REASONS, WE CONSIDER FIRST-TIME GRANTEES A HIGHLY IMPORTANT CATEGORY OF INVESTIGATORS WHO MUST BE ADEQUATELY SUPPORTED BY NIH AWARDS. IN 1982, ABOUT 8 PERCENT OF OUR AWARDEES WERE "FIRST-TIMERS" -- THIS, BY THE WAY, IS THE LOWEST THAT RATIO HAS BEEN IN A DECADE. IN FY '83, WHEN WE FUNDED 39 PERCENT OF STUDY SECTION APPROVED AWARDS, THIS FIGURE ROSE

SOME BUT PRECISE FIGURES ARE NOT YET AVAILABLE.

AT THE OTHER END OF THE GRANTEE SPECTRUM IS THE OUTSTANDING ESTABLISHED INVESTIGATOR FOR WHOM A MECHANISM IS NEEDED FOR PROVIDING LONGER TERM, MORE FLEXIBLE SUPPORT.

OUR SECOND MAJOR CHALLENGE LIES IN RESEARCH TRAINING. IN OUR VIEW, THE TRAINING AND RESEARCH PROGRAMS ARE SO CLOSELY INTERWOVEN AS TO BE PRACTICALLY INDIVISIBLE.

AT THE PRESENT TIME, THE STIPENDS AVAILABLE FOR SUPPORT OF NATIONAL RESEARCH SERVICE AWARD TRAINEES ARE PALTRY, WELL BELOW THOSE AVAILABLE IN OTHER FEDERAL RESEARCH TRAINING PROGRAMS. PREDOCTORAL STIPENDS SHOULD BE RAISED TO THE $8,100 THAT IS OFFERED BY THE NATIONAL SCIENCE FOUNDATION. ADDITIONAL TRAINING SLOTS SHOULD BE MADE AVAILABLE FOR THE NRSA PROGRAM TO BRING IT TO THE LEVEL RECOMMENDED BY THE NATIONAL ACADEMY OF SCIENCES. OVER A TWO-YEAR PERIOD, TRAINING POSITIONS SHOULD BE INCREASED TO ABOUT 10,500. INCREASES ARE ALSO NEEDED IN THE CAREER DEVELOPMENT PROGRAM AT A RATE OF 200 ADDED AWARDS A YEAR FOR THREE YEARS. TOTAL NEEDS TO BRING THE SUPPORT OF THESE PROGRAMS TO COMPETITIVE LEVELS AMOUNT TO ABOUT $84 MILLION, OR A 50 PERCENT INCREASE IN TRAINING FUNDS.

THE INTENSE COMPETITION FOR RESEARCH SUPPORT HAS INCREASINGLY TAKEN ITS TOLL OF THE AMATEUR OR UNDERTRAINED INVESTIGATOR. THE PROFESSIONALIZATION OF RESEARCH ACTIVITY HAS PROGRESSIVELY SELECTED AGAINST THE M.D. SCIENTIST WHO 15 YEARS AGO HAD A MUCH BETTER PROSPECT OF SUCCESS IN RESEARCH APPLICATIONS THAN THE PH.D. APPLICANT. CONCURRENTLY, THERE HAS BEEN A DECREASE IN THE NUMBER OF PHYSICIANS WHO ARE SEEKING RESEARCH TRAINING.

THE APPLICATION OF SCIENTIFIC ADVANCES TO MAINTAIN GOOD HEALTH AND TO PREVENT AND TREAT DISEASE IS ULTIMATELY THE RESPONSIBILITY OF THE PHYSICIAN. THE TRAINED CLINICAL INVESTIGATOR IS THE CRITICAL LINK BETWEEN THE LABORATORY AND THE HEALTH CARE PROVIDER. IN THE FACE OF THE EXPLOSIVE GROWTH OF BASIC KNOWLEDGE IN THE BIOMEDICAL SCIENCES WHICH HAS OPENED UP VAST OPPORTUNITIES FOR CLINICAL RESEARCH, THE SHORTFALL IN TRAINING OF CLINICAL INVESTIGATORS ASSUMES ADDITIONAL SIGNIFICANCE.

ANOTHER MATTER REQUIRING ATTENTION IS THE NEED TO REPLACE OR PURCHASE THE INCREASINGLY SOPHISTICATED INSTRUMENTS REQUIRED FOR TODAY'S RESEARCH. IT IS ESTIMATED THAT 20 MILLION DOLLARS A YEAR FOR FIVE YEARS IS NEEDED FOR

THE ACQUISITION OF LARGE-SCALE SHARED INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE THROUGH RESEARCH GRANTS OF SMALLER INSTRUMENTS. THE NIH HAS RECENTLY JOINED AN ONGOING STUDY BY THE NATIONAL SCIENCE FOUNDATION FOR THE PURPOSE OF SECURING A VALID CURRENT ASSESSMENT OF NATIONAL NEED.

FINALLY, EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND MORE RECENTLY BY THE NATIONAL EYE INSTITUTE, NIH STOPPED SUPPORTING FACILITIES AFTER 1969, AND CURRENTLY LACKS LEGAL AUTHORITY TO DO SO.

AS A CONSEQUENCE, MANY OF THE FACILITIES BENEFITING FROM THE MAJOR NIH CONSTRUCTION EFFORT -- THE HEALTH RESEARCH FACILTIES PROGRAM -- ARE MORE THAN 20 YEARS OLD, OR RAPIDLY APPROACHING THAT MARK.

RATHER THAN CALLING FOR ANY NEW MAJOR EXPANSION, THE REALISTIC AIM OF ANY NEW FEDERAL CONSTRUCTION PROGRAM SHOULD PROBABLY BE LESS AMBITIOUS. IT SHOULD, HOWEVER, INCLUDE NEW CONSTRUCTION TO REPLACE OUTMODED FACILITIES, TO RELIEVE OVERCROWDING, AND TO ACCOMMODATE CHANGING RESEARCH REQUIREMENTS, INCLUDING FACILITIES FOR DEALING WITH TOXIC

WASTES, FACILITIES TO (FOR?) LABORATORY ANIMALS, AND FOR MAJOR RENOVATION AND REPAIR OF INFERIOR FACILITIES. THERE IS A DEARTH OF GOOD INFORMATION ON CONSTRUCTION NEEDS, AND A CURRENT STUDY SIMILAR TO THAT BEING CONDUCTED ON INSTRUMENTATION DEFICITS IS SERIOUSLY NEEDED.

IT IS CLEAR THAT FOR A CONSTRUCTION PROGRAM TO MAKE ANY DIFFERENCE IN ADDRESSING THE NEEDS, THE MONIES APPROPRIATED WOULD HAVE TO BE SUBSTANTIAL. PAST APPROACHES WHICH HAVE LIMITED THE TOTAL FEDERAL CONSTRUCTION CONTRIBUTION TO UP TO SOME FIXED PERCENTAGE OF TOTAL COSTS MAY BE A REASONABLE CONDITION TO IMPOSE ON ANY NEW AUTHORITY DEVELOPED. IT IS ENCOURAGING TO NOTE THAT THE CONGRESS HAS RECOGNIZED THAT UNIVERSITIES AND OTHER INSTITUTIONS OF HIGHER LEARNING ARE REACHING A POINT WHERE THEY WILL NOT BE ABLE TO PARTICIPATE FULLY IN OUR COOPERATIVE RESEARCH ENDEAVOR WITHOUT ASSISTANCE.

ADDRESS*

by

JAMES B. WYNGAARDEN, M.D.**

IN LESS THAN FOUR YEARS, THE NATIONAL INSTITUTES OF HEALTH WILL CELEBRATE ITS 100TH ANNIVERSARY, COMMEMORATING ITS ESTABLISHMENT AS A ONE-ROOM LABORATORY AT THE MARINE HOSPITAL ON STATEN ISLAND IN 1887. FOR THE FOLLOWING 60 YEARS, IT WAS A RELATIVELY SMALL GOVERNMENT LABORATORY CARRYING OUT MOST OF ITS RESEARCH IN-HOUSE. IN SPITE OF ITS VERY MODEST PHYSICAL AS WELL AS FISCAL RESOURCES, THE EARLY ACCOMPLISHMENTS OF THE NIH WERE SUBSTANTIAL. THE STAFF OF THE NIH INCLUDED SOME OF THE GIANTS IN BIOMEDICAL RESEARCH OF THE TIME.

BUT THE NIH AS WE KNOW IT TODAY HAD ITS BEGINNINGS AT ALMOST THE SAME TIME THAT THE SOCIETY OF MEDICAL CONSULTANTS TO THE ARMED FORCES WAS ORGANIZED. THE SOCIETY AND THE NIH STEM FROM COMMON ROOTS, FOR IT WAS DURING WORLD WAR II THE LEADERS IN GOVERNMENT CAME TO A FULL RECOGNITION OF THE VALUE AND POTENTIAL OF BIOMEDICAL RESEARCH. AND YOUR FOUNDING MEMBERS HAD MUCH TO DO WITH BRINGING ABOUT AND FORTIFYING THAT CONVICTION. THEY WERE INVOLVED IN CARRYING OUT BIOMEDICAL RESEARCH AND APPLYING ITS FRUITS TO THE NEEDS OF THE MILITARY. AS YOU KNOW, THE RESULTS WERE BY ANY STANDARD SPECTACULAR. SUCH RAVAGING DISEASES AS YELLOW FEVER, DYSENTERY, TYPHUS, TETANUS, PNEUMONIA, AND MENINGITIS WERE ALL BUT CONQUERED BY PENICILLIN, THE SULFA DRUGS, NEW INSECTICIDES, BETTER VACCINES, AND IMPROVED HYGIENIC MEASURES.

THE STATISTICAL SUMMATION OF THIS APPLICATION OF NEW KNOWLEDGE SPEAKS FOR ITSELF AND IS WORTH REPEATING. THE DEATH RATE FROM ALL DISEASES IN THE ARMY, INCLUDING THE OVERSEAS FORCES, WAS REDUCED FROM 14.1 PER THOUSAND IN WORLD WAR I TO .6 PER THOUSAND IN WORLD WAR II. IT WAS BETTER THAN A TWENTY-THREEFOLD REDUCTION IN DEATH RATES.

SMALL WONDER THEN THAT WHEN LATE IN 1944 PRESIDENT ROOSEVELT BEGAN TO THINK OF THE TRANSITION TO PEACETIME, HE CALLED FOR ANOTHER WAR--THE WAR OF SCIENCE AGAINST DISEASE.

IN A LETTER TO HIS PRINCIPAL SCIENCE ADVISOR WRITTEN IN NOVEMBER 1944, THE PRESIDENT NOTED THAT THE ANNUAL DEATHS IN THIS COUNTRY FROM ONE OR TWO DISEASES

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*To the Society of Medical Consultants to the Armed Forces, National Naval Medical Center Commissioned Officers Open Mess, November 13, 1983.

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ALONE WERE FAR IN EXCESS OF THE NUMBER OF LIVES LOST IN COMBAT DURING THE WAR. HE SAW THIS AS A FACT THAT SHOULD MAKE US CONSCIOUS OF THE DUTY OWED TO FUTURE GENERATIONS, A DUTY TO CONTINUE SCIENTIFIC EXPLORATION IN THE FIELD OF HEALTH.

THEN HE POSED A SERIES OF QUESTIONS HAVING DIRECT RELEVANCE TO THE FUTURE OF BIOMEDICAL RESEARCH. HE ASKED, "WHAT CAN BE DONE NOW TO ORGANIZE A PROGRAM FOR CONTINUING IN THE FUTURE THE WORK WHICH HAS BEEN DONE IN MEDICINE AND THE RELATED SCIENCES?" HE THEN ASKED, "WHAT CAN THE GOVERNMENT DO NOW AND IN THE FUTURE TO AID RESEARCH ACTIVITIES BY PUBLIC AND PRIVATE ORGANIZATIONS?" AND THEN FINALLY THE PRESIDENT POSED A MOST SIGNIFICANT QUESTION, "CAN AN EFFECTIVE PROGRAM BE PROPOSED FOR DISCOVERING AND DEVELOPING SCIENTIFIC TALENT IN AMERICAN YOUTH SO THAT THE CONTINUING FUTURE OF SCIENTIFIC RESEARCH IN THIS COUNTRY MAY BE ASSURED . . . ?"

IN RESPONSE TO THE PRESIDENT'S SUGGESTIVE QUESTIONS, VANNEVAR BUSH IN 1945 SUBMITTED A LANDMARK REPORT ON THE PROGRAM FOR POSTWAR SCIENTIFIC RESEARCH TITLED, "SCIENCE--THE ENDLESS FRONTIER." THE ESSENCE OF THE REPORT AS IT PERTAINS TO MEDICINE IS CAPTURED IN ONE SENTENCE. DR. BUSH WROTE, "IT IS CLEAR THAT IF WE ARE TO MAINTAIN THE PROGRESS IN MEDICINE WHICH HAS MARKED THE LAST 25 YEARS, THE GOVERNMENT SHOULD EXTEND FINANCIAL SUPPORT TO BASIC MEDICAL RESEARCH IN THE MEDICAL SCHOOLS AND IN THE UNIVERSITIES THROUGH GRANTS BOTH FOR RESEARCH AND FOR FELLOWSHIPS."

THE WARTIME NATIONAL COMMITTEE ON MEDICAL RESEARCH HAD EXECUTED ABOUT 500 CONTRACTS FOR MEDICAL RESEARCH AT 120 DIFFERENT INSTITUTIONS. OVER 95 PERCENT OF THESE CONTRACTS WERE WITH UNIVERSITIES OR TEACHING HOSPITALS. WITH DEMOBILIZATION, THE NATIONAL COMMITTEE WENT OUT OF BUSINESS BUT INSTEAD OF TERMINATING THE ONGOING GRANTS AND CONTRACTS FOR MEDICAL RESEARCH, THEY WERE TURNED OVER TO THE TINY NATIONAL INSTITUTE OF HEALTH FOR ADMINISTRATION.

THE WARTIME LESSONS ABOUT THE VALUE OF RESEARCH HAD BEEN WELL LEARNED. THE CONGRESS AND THE ADMINISTRATION ALMOST AT ONCE BEGAN TO ADD TO THIS INITIAL NEST EGG OF SPONSORED RESEARCH. IN THE INTERVENING YEARS, THE TOTAL OF NIH GRANTS AND CONTRACTS, INITIALLY LESS THAN A MILLION DOLLARS, GREW BY A FACTOR OF MORE THAN 4,000 TO THE 1983 LEVEL OF ALMOST FOUR BILLION DOLLARS.

DURING THAT PERIOD, THE ORGANIZATION ALSO GREW. THE SCOPE OF THE BIOMEDICAL RESEARCH IT CONDUCTS AND SPONSORS HAS BEEN BROADENED TO COVER PRACTICALLY EVERY AREA OF HEALTH CONCERN. ITS SCIENTISTS IN BETHESDA, AS WELL AS THOSE SUPPORTED IN LABORATORIES ACROSS THE NATION AND IN MANY DIFFERENT PARTS

OF THE WORLD, ARE CARRYING OUT THE PURSUIT OF BASIC KNOWLEDGE ON AN UNPRECEDENTED SCALE. FOR IT HAS BEEN CLEAR THAT IF EFFECTIVE ASSAULTS ARE TO BE MADE ON THE MAJOR DISEASE PROBLEMS, MUCH MORE NEEDS TO BE KNOWN AT THE FUNDAMENTAL LEVEL.

IN RECENT YEARS THERE HAS BEEN A MARKED GROWTH IN THE RESEARCH COMMITMENTS OF PRIVATE INDUSTRY BUT FOR PERFECTLY GOOD REASONS THE MAJOR EMPHASIS OF SUCH RESEARCH HAS BEEN ON THE REFINEMENT AND DEVELOPMENT OF KNOWN MEASURES, NEW VACCINES, NEW PHARMACEUTICAL AGENTS AND OTHER MEANS FOR DIAGNOSIS AND TREATMENT.

THE INDISPENSABLE SEARCH AT THE FRONTIERS OF SCIENCE REMAINS A RESPONSIBILITY CARRIED OUT IN LARGE PART BY THE GOVERNMENT. IT IS ESTIMATED, FOR EXAMPLE, THAT THE NIH SUPPORTS 90 PERCENT OF THE BASIC BIOMEDICAL RESEARCH CONDUCTED IN AMERICAN UNIVERSITIES.

LET ME TURN FOR A MOMENT TO THE NIH ITSELF. ONE OF MY ASSOCIATES LIKES TO TELL HOW WHEN HE ATTENDED A RECEPTION HELD BY A BETHESDA BUSINESS ORGANIZATION WHERE HIS WIFE WORKED, HE WAS ASKED, BY ONE OF THE HOSTS, WHERE HE WORKED. HE REPLIED, "I'M AT NIH." THE HOST, TAKEN ABACK, SAID, "WHY, I THOUGHT YOU WORKED FOR THE GOVERNMENT."

IT IS TRUE THAT THE NIH IS NOT THE USUAL GOVERNMENT ORGANIZATION. THE PROPER NAME FOR OUR 300-ACRE SITE ACROSS THE STREET IS, OF COURSE, A "RESERVATION." ALMOST UNIVERSALLY, HOWEVER, WE REFER TO THE BETHESDA "CAMPUS." THE RESEMBLANCE TO A UNIVERSITY DOESN'T STOP THERE. THE NIH ORGANIZATION CLOSELY RESEMBLES THAT OF A UNIVERSITY. THE CONSTITUENT INSTITUTES ARE LIKE LARGE COLLEGES AND JUST AS INDEPENDENT OF THE CENTRAL NIH ADMINISTRATION AS MOST COLLEGES ARE OF CHANCELLORS AND PRESIDENTS. THE MORE THAN 2,000 SCIENTISTS ARE LIKE A FACULTY.

WE HAVE TREMENDOUS PARKING PROBLEMS AND A CONSTANT STRUGGLE TO MAINTAIN THE GREEN OPENNESS OF THE CAMPUS. THE BUILDINGS ARE MARKED IN MYSTERIOUS WAYS SO THAT VISITORS AND INDIGENOUS PERSONNEL ALIKE HAVE A HARD TIME FINDING THEIR WAY AROUND. WE HAVE A SERIES OF INTRAMURAL CONCERTS AND LECTURES AS WELL AS HUNDREDS OF SEMINARS AND WORKSHOPS EVERY YEAR. AT LEAST ONCE AN UNDERGROUND NEWSPAPER SURFACED ON CAMPUS. IN THE LATE SIXTIES AND SEVENTIES, THERE WERE ANTIWAR DEMONSTRATIONS. EARLIER THIS YEAR WE HAD AN ALL-DAY VISIT FROM DEMONSTRATORS OPPOSING THE USE OF ANIMALS IN RESEARCH. IN THE CAFETERIAS, ONE ENCOUNTERS A STIMULATING MIXTURE OF SCIENTISTS FROM MANY DISCIPLINES. ELEVATOR TALK RANGES FROM ARGUMENTS ABOUT MONOCLONAL ANTIBODIES TO HOPEFUL SPECULATION ON THE 1984 SUPERBOWL PROSPECTS OF THE REDSKINS.

SEARCH COMMITTEES ARE APPOINTED IN PRECISELY THE ACADEMIC TRADITION WHEN MAJOR STAFF VACANCIES ARE TO BE FILLED, AND THE ADVICE OF THE COMMITTEES IS HEEDED. WE HAVE INTRAMURAL SPORTS. OUR RUNNING CLUB HAPPILY NAMED "HEALTH'S ANGELS" IS QUITE ACTIVE.

WE LACK A STUDENT BODY AS SUCH AND HAVE NOT GONE OUT FOR FOOTBALL, EVEN THOUGH THE "NIH SHIFT," A TECHNICAL TERM WELL KNOWN IN SOME CIRCLES, SOUNDS AS IF IT CAME FROM THE GRIDIRON INSTEAD OF A LABORATORY. FURTHER, IT HAS BEEN ALLEGED THAT IN THE PAST SOME NIH DIRECTORS WERE SKILLFUL IN EXECUTING END RUNS AROUND THE DEPARTMENT OF HEALTH AND HUMAN SERVICES AND EVEN THE OFFICE OF MANAGEMENT AND BUDGET.

THESE ANALOGIES TO A UNIVERSITY HAVE NO PARTICULAR SIGNIFICANCE IN THEMSELVES OTHER THAN THE FACT THAT THEY REFLECT THE AGENCY'S ORIENTATION TOWARD AND CLOSE RELATIONSHIP WITH ACADEMIC INSTITUTIONS.

OCCASIONALLY A PERSON NOT FAMILIAR WITH THE BIOMEDICAL RESEARCH SCENE ASKS, "WHERE IS THE NIH?" THAT TURNS OUT TO BE A BETTER QUESTION THAN IT SEEMS. MORE THAN 80 PERCENT OF NIH RESEARCH ACTIVITY TAKES PLACE AWAY FROM THE BETHESDA CAMPUS. THERE ARE A FEW DIRECT OPERATIONS IN OTHER LOCATIONS--NOTABLY THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES IN THE RESEARCH TRIANGLE, NORTH CAROLINA--BUT BY FAR THE MAJOR SHARE OF NIH WORK IS CARRIED OUT BY NONFEDERAL SCIENTISTS IN SOME 1,200 MEDICAL SCHOOLS, UNIVERSITIES, AND HOSPITALS THAT RECEIVE GRANT AND CONTRACT AWARDS.

THE MANDATE OF THE NIH IS TO CONDUCT AND SUPPORT RESEARCH BUT, IN ORDER TO DO THIS, IT MUST ALSO BE CONCERNED WITH THE WELLBEING AND STABILITY OF THE RESEARCH INSTITUTIONS. THE TWO ELEMENTS, SUPPORT OF RESEARCH AND THE HEALTH OF THE RESEARCH INSTITUTION, ARE INSEPARABLY LINKED ONE TO THE OTHER. TO PUT IT EVEN MORE STRONGLY, THE FEDERAL GOVERNMENT--NIH--IN CARRYING OUT ITS RESEARCH MISSION, IS IN FACT DEPENDENT UPON THE INSTITUTIONS.

IN ACKNOWLEDGING THIS DEPENDENCE, I DO NOT UNDERESTIMATE THE ESSENTIAL ROLE PLAYED BY THE MASSIVE INTRAMURAL RESEARCH PROGRAM. WE HAVE IN BETHESDA THE WORLD'S LARGEST BIOMEDICAL RESEARCH LABORATORY. SOME OF YOU IN THIS AUDIENCE ARE MEMBERS OF OR LEAD THE TREMENDOUSLY PRODUCTIVE TEAMS OF INVESTIGATORS WHO MAKE UP THE INTRAMURAL NIH SCIENTIFIC COMMUNITY. THE INFLUENCE OF THAT COMMUNITY IS TRULY WORLDWIDE. FOR AT ANY GIVEN TIME, WORKING SIDE BY SIDE WITH OUR SCIENTISTS, THERE ARE LARGE NUMBERS OF GUEST WORKERS, VISITING SCIENTISTS, AND FELLOWS FROM ALMOST LITERALLY EVERYWHERE. CURRENTLY, 60 COUNTRIES ARE REPRESENTED BY THE MORE THAN 1,200 INVESTIGATORS NOW ACTIVE ON THE NIH CAMPUS.

OUR INTRAMURAL PROGRAM IS ALSO GREATLY STRENGTHENED BY CLOSE AND FRUITFUL COLLABORATION WITH LABORATORY AND CLINICAL SCIENTISTS WHO STAFF OUR NEIGHBORING ORGANIZATIONS, THE UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES AND THE REGIONAL NAVAL COMMAND.

INTRAMURAL NIH HAS ALSO MADE A LASTING MARK ON AMERICAN BIOMEDICAL RESEARCH AND ACADEMIC MEDICINE THROUGH THE "ALUMNI" WHO HAVE TRAINED OR WORKED IN OUR LABORATORIES. A STARTLING NUMBER OF KEY POSITIONS IN UNIVERSITIES, MEDICAL SCHOOLS, PRIVATE LABORATORIES, AND INDUSTRIAL RESEARCH ESTABLISHMENTS ARE HELD BY FORMER "NIHers."

IN THE PREFACE TO A BOOK NOW IN PREPARATION ABOUT INTRAMURAL NIH, LEWIS THOMAS WROTE ". . . ONE ASPECT OF THE INTRAMURAL PROGRAM DESERVES SPECIAL MENTION AND EMPHASIS. IT IS AS A TRAINING GROUND FOR YOUNG INVESTIGATORS WHO HAVE COME TO BETHESDA FOR THEIR POSTDOCTORAL EDUCATION IN RESEARCH, THAT THE INSTITUTION HAS ACHIEVED ITS MOST SINGULAR INFLUENCE ON THE PROGRESS OF AMERICAN SCIENCE. FOR THREE DECADES THE YOUNGEST AND BRIGHTEST CANDIDATES FOR CAREERS IN BIOMEDICAL RESEARCH HAVE COMPETED FOR THE OPPORTUNITY TO DO SCIENCE IN THIS PLACE. MOST OF THEM WORKED HERE FOR TWO OR THREEE YEARS AND THEN DEPLOYED OUT TO THE UNIVERSITIES TO CONTINUE IN RESEARCH, AND A HIGH PERCENTAGE OF THESE ALUMNI THEN TURNED INTO THE LEADERS OF ACADEMIC SCIENCE."

AS WE LOOK BACK OVER THE TWO PAST DECADES, THE DEVELOPMENT OF NIH REPRESENTS A REMARKABLE SUCCESS STORY. IT IS AN OUTSTANDING EXAMPLE OF HOW SUCCESSIVE CONGRESSES AND SUCCESSIVE ADMINISTRATIONS CAN WORK TOGETHER FOR A VITAL PURPOSE IN A SITUATION WHERE A DELICATE BALANCE MUST BE MAINTAINED BETWEEN THE PUBLIC'S UNDERSTANDABLE DEMAND FOR RESULTS FROM THE EXPENDITURE OF PUBLIC FUNDS AND SCIENCE'S INHERENT NEED FOR INDEPENDENCE AND ELBOW ROOM.

I CAN'T RESIST QUOTING JUST A BIT MORE FROM THE LEWIS PREFACE. HE SAID, ". . . IT LIFTS THE HEART TO LOOK CLOSELY AT ONE INSTITUTION CREATED BY THE UNITED STATES GOVERNMENT WHICH HAS BEEN ACHIEVING, SINCE ITS OUTSET, ONE SPECTACULAR, STIRRING SUCCESS AFTER ANOTHER. THE NATIONAL INSTITUTES OF HEALTH IS NOT ONLY THE LARGEST INSTITUTION FOR BIOMEDICAL SCIENCE ON EARTH; IT IS ONE OF THE NATION'S GREAT TREASURES. AS SOCIAL INVENTIONS FOR HUMAN BETTERMENT GO, THIS ONE IS STANDING PROOF THAT, AT LEAST ONCE IN A WHILE, GOVERNMENT POSSESSES THE CAPACITY TO DO SOMETHING UNIQUE, IMAGINATIVE, USEFUL, AND ALTOGETHER RIGHT."

RECENTLY THERE HAVE BEEN EXPRESSIONS OF CONCERN ABOUT THE FUTURE OF THE SCIENTIFIC ENTERPRISE AND A CERTAIN AMOUNT OF UNEASINESS ABOUT THE FINANCIAL FUTURE OF RESEARCH AS WELL AS ACADEMIC INSTITUTIONS. IT WOULD BE FOOLISH TO SAY

THAT WE HAVE NO PROBLEMS, BUT I HAVE A STRONG SENSE OF OPTIMISM ABOUT THE STATE OF SCIENCE AND THE STATE OF THE RESEARCH ENTERPRISE ITSELF.

THE SURGE OF DISCOVERY THAT WE HAVE SEEN IN THE BIOSCIENCES IN THE LAST DECADE OR SO IS WITHOUT PRECEDENT AND, IF ANYTHING, IS GATHERING STRENGTH. PROMISING DISCOVERIES HAVE QUICKLY BEEN TRANSFORMED INTO POWERFUL NEW MEASURES FOR THE DIAGNOSIS, TREATMENT, AND PREVENTION OF DISEASE. MAJOR NEW INDUSTRIES HAVE SPRUNG INTO BEING, MAKING USE OF THE RECOMBINANT DNA TECHNIQUES THAT ONLY TEN YEARS AGO WERE REVOLUTIONARY. IT IS AN EXCITING TIME, INDEED. I FEEL FORTUNATE AS I AM SURE YOU DO TO BE AN ACTIVE PARTICIPANT IN THE MATTERS OF SO MUCH REALIZED POTENTIAL AND HISTORICAL SIGNIFICANCE.

AND WITH IT ALL IS THE STRONG INTUITION THAT WE ARE ONLY BEGINNING TO SEE THE FRUITS OF EXPLORATION AT THE FRONTIERS. PERHAPS IT IS OUR PERCEPTION OF THE URGENT NEED TO MAINTAIN THE CURRENT MOMENTUM AND PACE OF DISCOVERY THAT IS THE SOURCE OF A CERTAIN NAGGING ANXIETY.

I BELIEVE WE CAN PREDICT WITH CONFIDENCE A CONTINUATION OF SCIENCE SOLELY ON THE ELEMENTAL GROUND OF THE INSATIABLE, UNCONTROLLABLE HUMAN DRIVE TO LEARN THINGS. THIS DRIVE ISN'T NEW BUT THE NEW THING THAT HAS HAPPENED IN THE PAST HALF CENTURY IS THE ENTHUSIASTIC ACCEPTANCE BY AMERICAN SOCIETY OF THE CONCEPT THAT MORE SCIENTIFIC KNOWLEDGE CAN LEAD TO RESULTS OF IMMENSE PRACTICAL VALUE.

IN THE FIELD OF MEDICINE, THE WISDOM OF INVESTING IN RESEARCH HAS BECOME AN ARTICLE OF FAITH, NOT JUST OF THE SCIENTIFIC AND PROFESSIONAL COMMUNITY, BUT OF THE PUBLIC AT LARGE.

THIS CONFIDENCE IS REFLECTED IN THE APPEALS BY THE VOLUNTARY HEALTH AGENCIES DIRECTED TO THE LAY PUBLIC. SUCH SOLICITATIONS FOCUS ON THE NEED FOR FUNDS FOR RESEARCH AS THE PRIME MEANS FOR ATTACKING DISEASE. THE RECURRENT CAMPAIGNS TO ADD NEW DISEASE-SPECIFIC INSTITUTES TO THE NATIONAL INSTITUTES OF HEALTH ARE ACTIONS BY TRUE BELIEVERS IN THE POWER OF RESEARCH. IN FACT, THE LAY LEADERS OF THESE INITIATIVES OFTEN HAVE MUCH GREATER CONFIDENCE IN THE IMMEDIATE EFFICACY OF RESEARCH THAN IS HELD BY THE MOST DEVOTED INVESTIGATOR IN THE FIELD. IN SPITE OF SOME OF THE ATTENDANT DIFFICULTIES THAT SUCH MOVEMENTS FOR NEW INSTITUTES IMPLY, I WOULD MUCH PREFER THE OCCASIONAL CLAMOR FOR A NEW INSTITUTE TO PUBLIC APATHY AND A LACK OF FAITH IN SCIENCE.

THIS CONFIDENCE IS HEARTENING, INDEED, BUT IT ALSO IMPLIES HEIGHTENED PUBLIC EXPECTATIONS FROM SCIENCE AND INCREASED RESPONSIBILITY FOR THOSE OF US WHO ARE ENGAGED IN THE RESEARCH ENTERPRISE.

IN THE CONDUCT OF RESEARCH, THE ANSWERS TO TODAY'S QUESTION USUALLY APPEAR IN THE COMPANY OF NEW AND MORE DIFFICULT PUZZLES. SUCCESSES IN OUR STRUGGLES

AGAINST HUMAN AILMENTS PERFORM A KIND OF SCREENING PROCESS SO THAT THE REMAINING PROBLEMS ARE EVER MORE RESISTANT. THIS IS THE ESSENCE OF THE CHALLENGES WE WILL BE FACING IN THE COMING YEARS.

WE MUST NOT RESPOND TO THIS EVER INCREASING CHALLENGE IN THE SAME WAY A MINOR OFFICIAL DID IN A SMALL SOUTHERN TOWN A FEW YEARS AGO. HE WAS THE LOCAL DOG CATCHER WHO HAD DECIDED TO GIVE UP HIS JOB AND HE APPEARED BEFORE THE CITY COUNCIL TO EXPLAIN WHY HE WAS RESIGNING. HE THANKED THE COUNCIL FOR RECENTLY RAISING THE BOUNTY TO A DOLLAR A DOG. THAT HAD HELPED, HE SAID, BUT HE STILL COULDN'T MAKE IT FINANCIALLY EVEN AFTER MOVING IN WITH HIS IN-LAWS. "THE PROBLEM," HE SAID, "IS THAT THE DOGS THAT ARE LEFT ARE THE HARD ONES TO CATCH."

PRESSURES, POLITICS, AND ETHICAL DECISIONS*

by

JAMES B. WYNGAARDEN, M.D.**

I AM HAPPY TO HAVE BEEN INVITED TO SPEAK TO YOU TODAY AND TO HAVE THIS OPPORTUNITY TO DISCUSS SOME MATTERS THAT PROBABLY HAVE NOT MUCH OCCUPIED YOUR THOUGHTS--CERTAINLY NOT ON A DAILY BASIS. THE STUDENTS AMONG YOU PROBABLY FOCUS YOUR CONCERNS ON THE THINGS OF THE MOMENT--ON YOUR NEXT EXAM, THE COURSE YOU'LL TAKE NEXT SEMESTER, OR WHAT YOU WILL DO UPON GRADUATION. THIS IS, OF COURSE, APPROPRIATE, NOT TO MENTION WISE. TODAY, IN MY TALK ABOUT PRESSURES, POLICY-MAKING AND ETHICS, I HOPE TO GIVE YOU A BROAD LOOK AT POLICY-MAKING IN BIOMEDICAL SCIENCE, IN PARTICULAR A VIEW OF NATIONAL POLICY-MAKING. THESE ARE MATTERS THAT OCCUPY A GREAT DEAL OF MY TIME AND ENERGY AND THAT OF MY STAFF AT THE NIH. I HOPE BY THE END OF MY TALK I WILL HAVE CONVINCED YOU THAT GOVERNMENT OFFICIALS DO NOT MAKE REGULATIONS, AND SET GUIDELINES AND POLICIES JUST TO CREATE WORK FOR UNIVERSITY ADMINISTRATIVE PERSONNEL, OR TO INFLATE THE COST OF CONDUCTING RESEARCH. WE MAKE THEM IN OUR STEWARDSHIP ROLE OVER PUBLIC TAX MONIES, AND TO PRESERVE THE FUTURE OF THE SCIENTIFIC ENDEAVOR IN THIS COUNTRY--AN ENDEAVOR WHICH, I MIGHT ADD, IS CHERISHED BY THE CONGRESS, THE ADMINISTRATION, AND IN LARGE PART, BY THE PUBLIC.

WHEN I SAY THAT WE MAKE POLICIES, REGULATIONS AND GUIDELINES, THE WORD "MAKE" IS WHOLLY INADEQUATE TO DESCRIBE THE PROCESS. TO MAKE A POLICY--LET US SAY ON PARTICIPATION OF HUMAN SUBJECTS IN RESEARCH--MAY REQUIRE FORMATION OF A SO-CALLED "COMMISSION" OR ADVISORY COMMITTEE TO STUDY THE MATTER; A PUBLIC HEARING OR MANY; INTERPRETATIONS OF LEGAL DECISIONS; REPORTS BY AUGUST BODIES; CONSULTATIONS WITH THEOLOGIANS, ETHICISTS, AND LEGAL "LIGHTS"; AND PUBLICATION IN THE FEDERAL REGISTER. IT MIGHT REQUIRE YEARS OF DEBATES--MOST OF THEM IN PUBLIC SESSION WITH REPRESENTATIVES OF THE MEDIA LISTENING IF THE TOPIC IS OF GENERAL INTEREST. ALL OF THESE MECHANISMS ARE NECESSARY TO INSURE CREDIBILITY, TO ASSURE THAT ALL SIDES-- AND THERE ARE NEVER JUST TWO--ARE HEARD BEFORE FINAL DECISIONS ARE MADE. THE POLICIES IN THEIR FINAL FORM TEND TO REFLECT THE PRACTICES OF THE BEST INSTITUTIONS--THEY ARE DERIVED FROM THE COMMUNITY ITSELF, GENERALIZED TO BE APPLIED MORE WIDELY, AND TESTED IN THE PUBLIC FORUM.

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ANOTHER GENERALITY ABOUT NATIONALLY-MADE POLICIES IS THAT THEY ARE NOT SET UP--AND COULD NEVER BE SET UP--TO TAKE OVER THE ETHICAL RESPONSIBILITIES OF THE INDIVIDUAL SCIENTIST OR THE JUDGMENT OF THE ACADEMIC INSTITUTION IN WHICH HE OR SHE IS WORKING. NIH, AS PRIME SUPPORTER OF BIOMEDICAL RESEARCH IN THIS COUNTRY, HAS HISTORICALLY LOOKED TO THE INDIVIDUAL SCIENTIST AND THE ACADEMIC INSTITUTION AS THE SEAT OF CREATIVITY. IN FORMULATING NECESSARY POLICIES, REGULATIONS AND GUIDELINES, THE NIH EVER HAS ITS EYE ON THE ULTIMATE EFFECTS OF ITS ACTIONS ON THE CREATIVE FORCES OF SCIENCE. THUS, NIH LEAVES MUCH GOVERNANCE TO THE INSTITUTIONS THEMSELVES. WE HAVE FOUND THAT LOCAL GOVERNANCE IS NOT ONLY THE BEST WAY TO HANDLE MATTERS CENTRAL TO THE CONDUCT OF SCIENCE, BUT IT HAS PROVEN TO BE ECONOMICAL AS WELL.

TO SOME, OF COURSE, ANY REGULATION, ESPECIALLY AT THE NATIONAL LEVEL, IS ANTITHETICAL TO CREATIVITY. REGULATION OF SCIENCE AND CREATIVITY IN SCIENCE ARE, TO THEM, CONTRADICTIONS IN TERMS (OXYMORONS). BUT IN FACT, THESE TWO CONCEPTS COEXIST AND EVEN DEPEND UPON ONE ANOTHER--THERE ARE CERTAIN LINES OF TENSION BETWEEN THE TWO. THIS TENSION SHOULD ALWAYS BE READJUSTED, BUT NEVER DONE AWAY WITH. IN A SOCIETY WHERE BIOMEDICAL RESEARCH FOR THE MOST PART DEPENDS UPON PUBLIC PATRONAGE, THE BIOMEDICAL ENTERPRISE COULD NOT EXIST AT THE EXTREMES OF EITHER TOTAL LAISSEZ FAIRE FOR THE INDIVIDUAL SCIENTIST OR WITH OVERLY RIGID PROCESSES OR GUIDELINES. THE EXTREMES OF EITHER COUNTERPOISE ARE DANGEROUS TO THE SCIENTIFIC ENTERPRISE, FOR EACH PRINCIPLE IN ITS EXTREME IS HIGHLY UNSTABLE AND VULNERABLE. IN MANY INSTANCES, HOWEVER, WHEN PUBLIC PRESSURE HAS INCREASED, IT HAS BEEN THE RESPONSIBILITY OF NIH TO STEP IN AND READJUST THE LINES OF TENSION SO THAT SCIENCE CAN CONTINUE. THE TIME HAS LONG PASSED WHEN MEMBERS OF THE BIOMEDICAL ESTABLISHMENT COULD TAKE THEIR NIH GRANT MONEY, ISOLATE THEMSELVES IN A LABORATORY, AND EXPECT CONTINUED UNDERSTANDING. CLEARLY, GOOD SCIENCE AND ADHERENCE TO ETHICAL PRINCIPLES ARE NOT INIMICAL. EXPERIENCE HAS SHOWN US THAT INVESTIGATORS AND INSTITUTIONS MOST INSISTENT UPON HIGH STANDARDS FOR SCIENTIFIC RIGOR ARE OFTEN THE MOST SENSITIVE TO THE WELFARE OF SUBJECTS OF RESEARCH.

WE AT NIH TAKE OUR LEADERSHIP ROLE VERY SERIOUSLY. HOW WELL NIH AND ITS PARTNERS IN RESEARCH--THE ACADEMIC INSTITUTIONS, INDUSTRY AND SCIENTIFIC ASSOCIATIONS--RESPOND TO THESE PRESSURES WILL AFFECT THE STRENGTH OF SCIENCE IN THE FUTURE. HOW WELL WE UTILIZE THE TOOLS AVAILABLE TO US IN IMPLEMENTING PHILOSOPHICAL PRINCIPLES WILL AFFECT THE SCIENTIFIC ENDEAVOR AS A WHOLE.

I DO NOT MEAN TO IMPLY THAT ADMINISTRATIVE REGULATIONS, GUIDELINES, AND RULES ARE THE ONLY INSTRUMENTS AVAILABLE TO EXECUTIVE LEADERS. THE POWERFUL INFLUENCE OF BUDGETARY DECISIONS AND THE WISE IMPLEMENTATION OF LEGISLATIVE LANGUAGE CANNOT BE UNDERESTIMATED. MOREOVER, GOVERNMENT SOMETIMES WORKS BEST BY NOT WORKING--THAT IS, BY BEING ONLY MINIMALLY INVOLVED WHEN THAT SEEMS TO BE NECESSARY AND PRUDENT. AN EXAMPLE IS THE GROWING TREND OF ACADEMIC-INDUSTRIAL COLLABORATIONS IN BIOMEDICAL SCIENCE. THESE RELATIONSHIPS ARE BREAKING NEW GROUND AND ARE LIKELY TO PRODUCE PROFOUND ADVANCES IN SCIENCE. YET, CONCERNS HAVE BEEN RAISED ABOUT THE INFLUENCE OF COMMERCIALIZATION ON THE CHOICE OF SCIENTIFIC QUESTIONS ADDRESSED BY FACULTY--ON THEIR SELECTION OF RESEARCH IDEAS, IF MARKET-ABILITY AND THE QUEST FOR FINANCIAL REWARDS DRIVE THEIR DECISIONS; ON OPEN EXCHANGE OF IDEAS; ON PROMPT AND OBJECTIVE PUBLICATION. IT IS OF EXTREME IMPORTANCE TO THE INTEGRITY OF THE ACADEMIC INSTITUTIONS THAT THESE RELATIONSHIPS WITH INDUSTRY ARE WELL MANAGED.

SOME HAVE SUGGESTED THAT NIH TAKE THE LEAD IN DEVELOPING PRINCIPLES AND GUIDELINES FOR SUCH INTERACTIONS. WE HAVE NOT DONE SO. WE BELIEVE THESE MATTERS LIE PRIMARILY AT THE UNIVERSITY/INDUSTRIAL INTERFACE. THE ISSUES PROMPTED BY THESE JOINT VENTURES, WE BELIEVE, ARE PRIMARILY MATTERS OF UNIVERSITY GOVERNANCE. WHILE NIH IS PREPARED TO ASSIST UNIVERSITIES AND COMMERCIAL ORGANIZATIONS TO STRENGTHEN THEIR INTERRELATIONSHIPS, WE DO NOT SEE OUR ROLE AS A CENTRAL ONE. NEVERTHELESS, TO THE EXTENT THAT FEDERAL FUNDS ARE INVOLVED, WE OF COURSE WILL STRIVE CONTINUOUSLY TO ENSURE THAT THE PUBLIC INTEREST IS APPROPRIATELY SERVED.

BEFORE I TALK ABOUT MATTERS AFFECTING THE CONDUCT OF INDIVIDUAL RESEARCH PROJECTS AND THE FORMULATION OF REGULATIONS AND GUIDELINES PERTAINING TO THEM--FOR EXAMPLE, THOSE ON ANIMAL WELFARE, DNA RECOMBINATION, HUMAN SUBJECTS PARTICIPATION, AND MISCONDUCT IN SCIENCE--I WANT TO SPEAK OF ANOTHER TYPE OF PRESSURE BROUGHT UPON BIOMEDICAL SCIENCE. THESE PUBLIC EFFORTS YOU MIGHT CALL "POSITIVE PRESSURES" BECAUSE THEY CALL FOR MORE RESEARCH. YET, THESE PRESSURES CAN TEND TO FRAGMENT, AND COULD HAVE AN UNTOWARD EFFECT UPON SCIENCE IN THE LONG RUN, ESPECIALLY WHEN FEDERAL BUDGETS ARE CONSTRAINED. THESE PRESSURES GROW OUT OF CONFIDENCE--PUBLIC CONFIDENCE IN THE WISDOM OF INVESTING IN RESEARCH REFLECTED IN APPEALS BY VOLUNTARY HEALTH AGENCIES DIRECTED TO THE LAY PUBLIC AND THE CONGRESS. THE RECURRENT CAMPAIGNS TO ADD NEW DISEASE-SPECIFIC INSTITUTES TO THE NIH ARE, IN MOST CASES, ACTIONS BY TRUE BELIEVERS IN THE POWER OF RESEARCH.

BUT IT IS RATHER IRONIC THAT JUST WHEN SCIENCE IS CONVERGING--WHEN PREVIOUSLY SEPARATE SCIENTIFIC DISCIPLINES--FOR EXAMPLE, ANATOMY, PHYSIOLOGY, PHARMACOLOGY, MICROBIOLOGY, BIOCHEMISTRY AND PATHOLOGY--ARE MERGING IN A COMMON LANGUAGE OF CHEMISTRY--THERE ARE INCREASED EFFORTS BY SPECIAL INTEREST GROUPS TO TARGET RESEARCH FUNDING AT NARROW AREAS. SUCH PRESSURES BY SINGLE ISSUE ADVOCATES DAMAGE SCIENCE AS A WHOLE, AND ARE GROWING TO ALARMING LEVELS IN RESPONSE TO INCREASING COMPETITION FOR LIMITED RESOURCES. THIS IS COUNTER TO THE FLOW OF SCIENCE AND DISTURBING TO THE CONFLUENCE OF THE KNOWLEDGE BASE. OVER THE PAST TEN YEARS, THERE HAVE BEEN MORE THAN 15 LEGISLATIVE PROPOSALS TO ESTABLISH NEW NIH INSTITUTES AND NUMEROUS PROPOSALS TO SET ASIDE FUNDS OR OTHERWISE TO EARMARK APPROPRIATIONS FOR CERTAIN PROGRAMS RELATED TO SPECIFIC DISEASES OR SYSTEMS OF THE BODY.

NIH HAS OPPOSED LEGISLATION TO CREATE NEW INSTITUTES AND OTHER LEGISLATION TENDING TO FRAGMENT. WE OPPOSE THESE PROPOSALS NOT ONLY BECAUSE OF THEIR ADVERSE EFFECTS ON ADMINISTRATIVE COSTS AND FLEXIBILITY, BUT ALSO BECAUSE THE COMPARTMENTALIZATION THEY ESTABLISH IS COUNTER TO THE DIRECTION IN WHICH SCIENCE IS MOVING. AT A TIME WHEN WE CAN CONFIDENTLY PREDICT UNUSUALLY RAPID MOVEMENT IN SCIENCE, BUT CANNOT PREDICT JUST WHERE THAT PROGRESS WILL OCCUR, WE NEED THE MAXIMUM FLEXIBILITY FOR MARSHALING FINITE RESOURCES FOR SUPPORT OF SCIENCE. ON THE OTHER HAND, WE SHOULD NOT BE SHORTSIGHTED. PERHAPS THERE IS A BETTER WAY TO ORGANIZE THE SUPPORT OF BIOMEDICAL RESEARCH IN THIS COUNTRY. LAST JUNE, NIH ASKED THE NATIONAL ACADEMY OF SCIENCES TO MAKE AN OBJECTIVE STUDY OF THE ORGANIZATIONAL STRUCTURE OF THE NIH AND, CONSIDERING SCIENTIFIC DEVELOPMENTS AND ECONOMIC REALITIES, MAKE RECOMMENDATIONS TO US. OUT OF THIS COULD GROW POLICIES OF THE FUTURE.

THE HISTORY OF PUBLIC PRESSURES TO PROTECT HUMAN SUBJECTS OF RESEARCH IS A LONG AND INTERESTING ONE, BUT I WOULD LIKE TO FOCUS ON ONE SMALL AND IMPORTANT BIT OF THAT HISTORY--FOR A SUSTAINING LESSON WAS LEARNED. BY 1966, NIH HAD DEVELOPED A POLICY FOR THE ENTIRE PUBLIC HEALTH SERVICE THAT REQUIRED CERTAIN BASIC FEATURES: REVIEW BY AN INDEPENDENT COMMITTEE, INFORMED CONSENT, A FAVORABLE RISK/BENEFIT RATIO AND ADEQUATE SAFEGUARDS FOR SUBJECTS. BUT THIS, APPARENTLY, WAS NOT SUFFICIENT. PUBLIC PRESSURE BEGAN TO BUILD AND SUDDENLY--IT SEEMED--THERE WAS HEIGHTENED CONCERN FOR SPECIAL SUBJECTS OF RESEARCH. LARGELY STIMULATED BY CONGRESSIONAL HEARINGS, NEWSPAPER ARTICLES BEGAN TO APPEAR PROMINENTLY QUESTIONING THE NEED FOR AND ETHICAL ASPECTS OF RESEARCH INVOLVING PRISONERS, FETUSES, THE MENTALLY INFIRM, AND CHILDREN. THERE WERE REPORTS

QUESTIONING THE ETHICAL GROUNDING OF USING INSTITUTIONALIZED MENTALLY RETARDED CHILDREN IN INFECTIOUS DISEASE STUDIES. CLAIMS WERE MADE THAT POOR BLACK MEN IN TUSKEEGEE HAD BEEN LEFT TO SUFFER WITH SYPHILIS FOR THE SAKE OF RESEARCH INTERESTS ALTHOUGH A TREATMENT WAS AVAILABLE, AND THERE WERE HORROR STORIES OF POSSIBLY VIABLE FETUSES BEING USED IN RESEARCH. WHILE THE SCIENTIFIC COMMUNITY FOR THE MOST PART AGREED THAT THESE SPECIAL SUBJECTS REQUIRED SPECIAL PROTECTIONS, THEY FEARED THAT ATTENTION TO THE MATTER WOULD TAINT PUBLIC OPINION OF RESEARCH--ESPECIALLY CLINICAL RESEARCH--AND THAT LEGISLATION MIGHT HANDICAP RESEARCH INVOLVING HUMAN SUBJECTS. OUT OF THE LEGISLATION THAT FINALLY PASSED IN 1974, EMERGED A COMMISSION--OFTEN TERMED THE HUMAN SUBJECTS COMMISSION--THAT WOULD MAKE RECOMMENDATIONS TO THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ON THESE MATTERS. TO FORM A COMMISSION WAS NOT A RARE POLITICAL MOVE AT THE TIME--THEY WERE COMMON. COMMISSIONS ARE OFTEN USED ADMINISTRATIVELY TO RELEASE PRESSURE THAT HAS BUILT BEHIND A PARTICULAR CIRCUMSTANCE. THE ADVISORY BODY QUIETLY DOES ITS WORK, THEN, WITHOUT FANFARE, DELIVERS ITS RECOMMENDATIONS TO THE ADMINISTRATION OR CONGRESS WHICH CAN EITHER ACCEPT, REJECT OR MODIFY THEM WITH LITTLE PUBLIC ATTENTION. BUT THIS COMMISSION WAS DIFFERENT. RIGHT FROM THE START, THE MEMBERS--ALL NON-FEDERAL PEOPLE--AGREED TO WORK FULLY IN THE PUBLIC EYE--WITH REPORTERS ATTENDING THEIR MEETINGS AND EVEN ACCOMPANYING THEM ON FIELD TRIPS TO PRISONS AND MENTAL INSTITUTIONS. ALL DRAFT MATERIAL WAS AVAILABLE TO THE PUBLIC AT ALL TIMES; OPEN HEARINGS WERE HELD AROUND THE COUNTRY. ALL WHO OBSERVED THE COMMISSION OVER ITS YEARS IN OPERATION AGREED THAT A GOOD MEASURE OF THE CREDIBILITY IT EARNED AMONG THE SCIENTIFIC COMMUNITY AND THE GENERAL PUBLIC WAS DUE TO THE OPENNESS WITH WHICH IT FACED ITS ASSIGNMENT.

AS FAR AS SUBSTANCE IS CONCERNED, THE COMMISSION HAS BEEN LARGELY RESPONSIBLE FOR THE ADDED EMPHASIS GIVEN IN FEDERAL REGULATIONS TO THREE ETHICAL PRINCIPLES OF HUMAN SUBJECTS RESEARCH: RESPECT, BENEFICENCE, AND JUSTICE. IN ADDITION TO EMPHASIZING CONCERN FOR PARTICULARLY VULNERABLE GROUPS OF RESEARCH SUBJECTS, THE COMMISSION ALSO ADDED A NEW MEASURE OF SENSITIVITY TO MATTERS OF PRIVACY AND CONFIDENTIALITY, ESPECIALLY IN BEHAVIORAL RESEARCH.

FROM THE EXPERIENCE OF THE HUMAN SUBJECTS COMMISSION, I THINK THE SCIENTIFIC COMMUNITY AND ESPECIALLY GOVERNMENT POLICY MAKERS LEARNED AN IMPORTANT LESSON--THAT THE PUBLIC IS CAPABLE OF PARTICIPATING IN POLICY-MAKING RELATING TO BIOMEDICAL SCIENCE AND THAT, UNLESS SPECIAL CIRCUMSTANCES PERTAIN, SUCH DELIBERATIONS SHOULD BE CONDUCTED IN PUBLIC FORUM, WITH ALL CONCERNED OFFERED THE

OPPORTUNITY TO COMMENT. I WILL NOT TAKE THE TIME TO EXPLAIN IN DETAIL THE PROCEDURES AND REGULATIONS NIH HAS EVOLVED OVER THE YEARS TO PROTECT HUMAN SUBJECTS PARTICIPATING IN NIH-SUPPORTED AND CONDUCTED RESEARCH. I WANT ONLY TO POINT OUT THAT THE FUNDAMENTAL SOUNDNESS AND WORKABILITY OF THE POLICIES HAVE BEEN REAFFIRMED REPEATEDLY. NIH HAS COME TO A POINT WHERE WE ARE REFINING OUR GUIDELINES, HELPING INSTITUTIONS TO INTERPRET THEM, AND TRYING TO FIND WAYS PERIODICALLY TO REVISE AND STRENGTHEN OUR PROCEDURES. THE REAL FOCUS FOR HUMAN SUBJECTS PROTECTION NOW LIES AT THE INSTITUTION ITSELF--WITH THE INSTITUTIONAL REVIEW BOARDS OR HUMAN SUBJECTS REVIEW COMMITTEES WHERE CASE-BY-CASE DECISIONS ARE MADE ON PROPOSED RESEARCH PROJECTS. NATIONAL AND LOCAL PROCEDURES ARE A MEANS TO AN END; THEY ARE NOT AN END IN THEMSELVES. THE PROCEDURES SET UP FOR NATIONAL REVIEW AND LOCAL POLICIES ARE THE OPPORTUNITY, THE OCCASION TO EXERCISE PROFESSIONAL JUDGMENT. TO THE NON-SCIENTIFIC WORLD, THE PROCEDURES DEMONSTRATE SYSTEMATIC, CAREFUL, JUDICIOUS MEASURES IN OUR STEWARDSHIP OF THE RIGHTS AND WELFARE OF INDIVIDUALS.

IN THE PAST THREE YEARS OR SO, THE SCIENTIFIC COMMUNITY AND THE PUBLIC HAVE BEEN SHOCKED BY WHAT SEEMS TO BE AN OUTBREAK OF MISCONDUCT IN SCIENCE. IT IS PARTICULARLY CONFOUNDING THAT FRAUD AND OTHER MISREPRESENTATION SHOULD INFECT THE SCIENTIFIC ENDEAVOR WHEN THE SEARCH FOR TRUTH IS THE DRIVING FORCE BEHIND SCIENTIFIC PURSUIT. SUCH EPISODES PRESENT SPECIAL DILEMMAS FOR BOTH THE PATRONS AND PRACTITIONERS OF RESEARCH, ESPECIALLY SINCE THE RESEARCH ENTERPRISE TODAY DEPENDS LARGELY UPON PUBLIC SUPPORT.

ALTHOUGH FRAUD IN SCIENCE IS NOT A NEW PHENOMENON, THERE IS NO QUESTION THAT THE INCIDENCE OF <u>REPORTED</u> MISCONDUCT HAS INCREASED DRAMATICALLY IN RECENT YEARS. UNTIL ABOUT THREE YEARS AGO, NIH RECEIVED SO FEW REPORTS OF MISCONDUCT THAT IT WOULD NEVER HAVE BEEN IDENTIFIED AS A TOPIC OF MAJOR CONCERN TO RESEARCH ADMINISTRATORS. IN THE PAST THREE YEARS, HOWEVER, NIH HAS RECEIVED AN AVERAGE OF TWO REPORTS OF MISCONDUCT PER MONTH; ABOUT HALF OF THOSE HAVE PROVEN TO BE FACTUAL, AND OF THOSE, SOME REFLECTED NOT FRAUDULENT INTENT, BUT SOME ERROR IN METHODOLOGY, SLOPPY TECHNIQUE, OR FAILURE TO DEVELOP AND COMMUNICATE APPROPRIATE POLICIES AT THE INSTITUTIONAL LEVEL.

VIEWED AGAINST A DENOMINATOR OF MORE THAN 20,000 NIH AWARDS ANNUALLY, THE NUMBER OF REPORTED MISCONDUCT INCIDENTS IS SMALL, ALMOST INSIGNIFICANT. INSIGNIFICANT IN NUMBER, BUT NOT IN IMPACT. THE MERE FACT THAT THE INCIDENTS OF WRONG-DOING IN SCIENCE RECEIVE SO MUCH MEDIA ATTENTION IS A TESTIMONIAL TO THEIR

RARITY. THE REPORTS HAVE GIVEN RISE TO WELL-FOUNDED CONCERNS ABOUT THE EFFICACY OF TRADITIONAL PRACTICES OFTEN CITED AS SAFEFUARDS AGAINST MISCONDUCT--PEER REVIEW OF RESEARCH PROPOSED FOR FUNDING OR PUBLICATION AND REPLICATION OF SIGNIFICANT FINDINGS.

THESE TRADITIONAL SAFEGUARDS ARE BASED ON THE ASSUMPTION THAT INDIVIDUAL INVESTIGATORS, WHILE PERHAPS ERRING IN METHODOLOGY OR THEORY, ARE HONEST AND WELL-INTENTIONED. THEY ARE NOT DESIGNED TO DETECT CLEVER, SYSTEMATIC CHEATING. THE REALIZATION THAT TRADITIONAL SAFEGUARDS OF SCIENCE CANNOT ENTIRELY PREVENT MISCONDUCT HAS BEEN ACCOMPANIED BY INCREASING EVIDENCE THAT AWARDEE INSTITUTIONS AND THE NIH ARE OFTEN ILL-PREPARED TO DEAL WITH ALLEGATIONS OR EVIDENCE OF WRONGDOING. UNTIL RECENTLY, WE HAVE BEEN ABLE TO TREAT SUCH INCIDENTS AS ISOLATED EVENTS, EMPLOYING AD HOC PROCEDURES FOR EACH CASE.

BUT IT HAS BECOME APPARENT THAT MORE EXPLICIT AND PREDICTABLE PROCEDURES ARE NEEDED TO ENABLE THE NIH (AND OTHER FUNDING AGENCIES) TO DEAL WITH ALLEGATIONS OR EVIDENCE OF MISCONDUCT. HERE THE REAL PROBLEM FOR POLICY MAKERS WAS TO DEAL WITH THE CONFLICTING DEMANDS OF ACCOUNTABILITY AND FISCAL STEWARDSHIP ON THE ONE HAND, AND DUE PROCESS AND PROTECTION OF INDIVIDUAL PRIVACY ON THE OTHER HAND. SO MUCH IS AT STAKE WHEN ALLEGATIONS ARE MADE: THE REPUTATIONS OF PRESTIGIOUS INSTITUTIONS, THE SCIENTIFIC CAREERS OF INDIVIDUAL INVESTIGATORS (MAYBE EVEN LIVELIHOOD FOR THEIR FAMILIES), THE REPUTATIONS OF THOSE MAKING ALLEGATIONS, AND THE CREDIBILITY OF THE NIH IN ITS STEWARDSHIP OVER PUBLIC MONIES. AND PERHAPS EVEN MORE IMPORTANT IN THE LONG RUN, THE PUBLIC'S CONTINUED SUPPORT FOR THE SCIENTIFIC ENDEAVOR.

BASED ON EXPERIENCE WITH EARLIER INCIDENTS AND INPUT FROM THE SCIENTIFIC COMMUNITY, NIH HAS DEVELOPED CERTAIN POLICIES AND PROCEDURES UNDERSCORING THE INSTITUTIONS' RESPONSIBILITY TO TAKE PROMPT AND APPROPRIATE ACTION WHEN MISCONDUCT IS KNOWN OR SUSPECTED AND TO INFORM THE NIH WHEN THE MATTER IS JUDGED TO BE SERIOUS ENOUGH TO WARRANT AN INVESTIGATION. HERE AGAIN, AS IN HUMAN SUBJECTS PROTECTION, A MAJOR FOCUS IS AT THE INSTITUTIONAL LEVEL. AND AGAIN, THERE IS OBVIOUSLY NO WAY TO REGULATE FULLY THE PROFESSIONAL INTEGRITY OF INDIVIDUAL SCIENTISTS.

THE POLICY FORMULATION SURROUNDING RECOMBINANT DNA RESEARCH MAKES AN INTERESTING CASE STUDY. I WILL NOT TAKE TIME TO DISCUSS THIS IN DETAIL, BUT I THINK AN OVERVIEW WILL BE OF SPECIAL INTEREST TO THIS GROUP BECAUSE QUESTIONS

ABOUT THE SAFETY OF RECOMBINANT DNA WORK RESURFACED LATELY WHEN RESEARCHERS AT BERKELEY SOUGHT PUBLIC SANCTION TO USE GENETICALLY MODIFIED MICROORGANISMS IN CONTROL OF FROST DAMAGE IN EXPERIMENTS INVOLVING CONTROLLED PLANTING OUT-OF-DOORS.

BACK IN 1973, WHEN FEW--CERTAINLY NOT THE GENERAL PUBLIC--KNEW VERY MUCH ABOUT THE PROMISES AND POSSIBLE PERILS OF RECOMBINANT DNA RESEARCH, SCIENTISTS WORKING IN THE FIELD REQUESTED A VOLUNTARY "MORATORIUM" ON SUCH WORK WHILE QUESTIONS OF PUBLIC SAFETY WERE FURTHER EVALUATED. THEY ALSO PROPOSED THAT THE NIH DEVISE GUIDELINES TO BE FOLLOWED BY INVESTIGATORS WORKING WITH POTENTIALLY HAZARDOUS RECOMBINANT DNA MOLECULES. IMPELLED BY PUBLIC, SCIENTIFIC, AND CONGRESSIONAL PRESSURE ATTENDING THE MATTER, THE NIH--WHICH TRADITIONALLY HAS SHUNNED A REGULATORY ROLE--RATHER RELUCTANTLY TOOK ON RESPONSIBILITY FOR ORGANIZING A MECHANISM FOR SETTING SAFETY GUIDELINES. THE NIH RECOMBINANT DNA ADVISORY COMMITTEE (CALLED RAC), INITIALLY MADE UP OF NON-FEDERAL ADVISORS, MOSTLY SCIENTISTS, MET FOR THE FIRST TIME--IN PUBLIC SESSION--IN FEBRUARY 1975 TO BEGIN TO DEVELOP PROPOSED GUIDELINES FOR RECOMBINANT DNA RESEARCH CARRIED OUT WITH NIH FUNDING. FOLLOWING A GREAT DEAL OF PUBLIC COMMENT AND DISCUSSION ON THE PROPOSALS, NIH ADOPTED INITIAL GUIDELINES IN JULY 1976. BASICALLY THEY CONSISTED OF A LISTING OF PROHIBITED EXPERIMENTS AND DESCRIBED IN GREAT DETAIL FOUR LEVELS OF PHYSICAL CONTAINMENT AND THREE LEVELS OF BIOLOGICAL CONTAINMENT NECESSARY FOR CERTAIN KINDS OF EXPERIMENTS. THEY ALSO SET DOWN THE ROLES AND RESPONSIBILITIES OF THE SCIENTIST, HIS OR HER INSTITUTION, AND THE INSTITUTION'S BIOSAFETY COMMITTEE (WHICH IS RATHER ANALAGOUS TO THE INSTITUTIONAL REVIEW BOARDS RELATING TO HUMAN SUBJECTS PROTECTION). THUS, THE GUIDELINES MATCHED THE PRINCIPLES NIH GENERALLY FOLLOWS IN MAKING POLICY THAT RELATES TO THE PUBLIC--THEY WERE MADE IN PUBLIC WITH PUBLIC PARTICIPATION; THEY PERMITTED RESEARCH TO CONTINUE WITH MINIMAL CONSTRAINTS YET PROTECTED THE PUBLIC INTEREST; AND THEY LEFT A GOOD MEASURE OF RESPONSIBILITY AT THE INSTITUTIONAL LEVEL. THE NEW GUIDELINES ALSO SERVED TO RELEASE PUBLIC PRESSURES ON THE MATTER. THERE WERE STILL SOME UNFORTUNATE MEDIA STORIES ABOUT POTENTIAL DANGERS OF SUCH RESEARCH, AND SOME LOCAL COMMUNITIES STILL WANTED NO SUCH RESEARCH CONDUCTED IN THEIR LOCALES. BUT FOR THE MOST PART, THE MEDIA BEGAN TO FOCUS ON THE POTENTIAL BENEFITS OF THIS TYPE OF RESEARCH. THE CONGRESS WAS SO INTERESTED IN THE SUBJECT THAT IN THE 95TH CONGRESS (1976-77), NO FEWER THAN 16 DIFFERENT BILLS

AROSE ON THE TOPIC OF RECOMBINANT DNA. MANY OF THEM CALLED FOR A NATIONAL LAW MAKING THE NIH GUIDELINES MANDATORY FOR PRIVATE INDUSTRY. IN FACT, NO LAW WAS ENACTED, SO THAT NOW, INDUSTRY ADHERENCE TO THE GUIDELINES IS VOLUNTARY.

THE NIH POLICY ON DNA RECOMBINANT WORK HAS FOLLOWED ANOTHER IMPORTANT PRINCIPLE--THAT OF FLEXIBILITY--SO THAT CHANGES IN OUR KNOWLEDGE OF THIS NEW SCIENCE COULD BE ACCOMMODATED IN THE GUIDELINES. IN 1978, MAJOR CHANGES WERE MADE IN THE GUIDELINES TO REFLECT EXPERIENCES WITH THE SAFETY OF DNA RECOMBINATION. MOREOVER, A PROCEDURE WAS DEVELOPED SO THAT THE GUIDELINES COULD BE REVISED ON AN ONGOING BASIS.

IT IS INTERESTING THAT AS LONG AS THE RAC MET IN PUBLIC, OPEN SESSION, PUBLIC PRESSURES SEEMED TO SUBSIDE. MORE RECENTLY, THE RAC HAS HAD TO CLOSE PORTIONS OF MEETINGS TO REVIEW PROPOSALS--CONTAINING PROPRIETARY INFORMATION--VOLUNTARILY SUBMITTED BY INDUSTRY. THIS HAS PROMPTED A FLURRY OF NEWSPAPER ARTICLES OVER A LAWSUIT TO STOP CERTAIN AGRICULTURAL USES OF GENETICALLY-ALTERED ORGANISMS IN CALIFORNIA, FOCUSED ON THE SO-CALLED "SECRET" RAC MEETINGS. THE NEED TO MEET IN CLOSED SESSION, COUPLED WITH THE FACT THAT RESEARCHERS ARE BEGINNING TO MOVE SOME EXPERIMENTS FROM THE LABORATORY INTO THE ENVIRONMENT, HAS PROVOKED NEW SIGNS OF PUBLIC CONCERN ABOUT RECOMBINANT DNA RESEARCH. ONCE AGAIN, THE SITUATION IS RIPE FOR GENERATION OF WHAT WE BELIEVE TO BE UNFOUNDED PUBLIC FEARS.

THE FINAL ISSUE I WANT TO DISCUSS TODAY IS A MOST IMPORTANT ONE FOR THE FUTURE OF SCIENCE. IT IS NOT NEW, BUT IT IS CERTAINLY CURRENT. THE PUBLIC PRESSURE REGARDING RESEARCH INVOLVING ANIMALS IS FAMILIAR TO ALL OF YOU IN CALIFORNIA, FOR CALIFORNIA IS AN ACTIVE PRESSURE POINT ON THIS ISSUE. THERE IS NO QUESTION THAT BIOMEDICAL RESEARCH CANNOT CONTINUE TO PROGRESS WITHOUT THE USE OF LABORATORY ANIMALS. WHILE IT IS TRUE THAT COMPUTER MODELING AND PROCEDURES IN VITRO MAY EVENTUALLY REPLACE ANIMALS IN SOME TOXICOLOGICAL TESTING, THE INVOLVEMENT OF ANIMALS TO DEMONSTRATE THE RESPONSE OF BIOLOGICAL SYSTEMS AND ORGANISMS TO CAREFULLY MEASURED INTERVENTIONS IS AND WILL REMAIN CENTRAL TO THE RESEARCH ENTERPRISE. VIRTUALLY EVERY MAJOR MEDICAL ADVANCE IN THIS CENTURY HAS DEPENDED UPON ANIMAL EXPERIMENTATION, AS SHOWN BY THE PROGRESS AGAINST DISORDERS SUCH AS CANCER, KIDNEY DISEASE, BLINDNESS, HEPATITIS AND HEART DISEASE. AT THE SAME TIME, OF COURSE, IT IS A MORAL IMPERATIVE THAT ANIMAL EXPERIMENTATION BE DONE IN THE MOST EFFECTIVE CONSERVATIVE AND HUMANE MANNER.

IT IS INTERESTING THAT ALTHOUGH THE ANIMAL WELFARE POLICY OF THE PUBLIC HEALTH SERVICE IS OLDER THAN THE POLICY FOR THE PROTECTION OF HUMAN SUBJECTS, THE PARTICIPATION OF HUMANS IN RESEARCH IS NOW RARELY A MATTER OF PUBLIC CONFLICT. WE AT NIH RECEIVE MUCH MORE MAIL FROM THE PUBLIC REGARDING ANIMAL EXPERIMENTATION THAN ON RESEARCH INVOLVING HUMAN SUBJECTS. LOOKING TO HISTORY FOR GUIDANCE, WE MIGHT TAKE A LESSON FROM THE POLICY-MAKING SURROUNDING RESEARCH ON HUMAN SUBJECTS--PERHAPS WE NEED A GREATER PUBLIC FORUM ON THE SUBJECT OF ANIMALS INVOLVED IN RESEARCH. THE HUMAN SUBJECTS PROTECTIONS NOW IN PLACE REFLECT A BROAD CONSENSUS OF THOSE CONCERNED WITH THE RIGHTS AND WELFARE OF HUMAN RESEARCH SUBJECTS; THE GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS AND THE PRINCIPLES FOR USE OF ANIMALS REFLECT A CONSENSUS WITHIN THE SCIENTIFIC COMMUNITY, BUT THEY DO NOT YET REPRESENT A CONSENSUS OF THOSE NUMEROUS GROUPS AND ASSOCIATIONS CONCERNED WITH ANIMAL WELFARE. THIS IS CERTAINLY REFLECTED IN THE FACT THAT THE 97TH CONGRESS HAS CONSIDERED NO FEWER THAN FIVE LEGISLATIVE INITIATIVES CONCERNING USE OF ANIMALS IN RESEARCH. IN ADDITION, 23 STATES HAVE PENDING LEGISLATION RELATING TO ANIMAL RESEARCH AND TESTING, AND THREE CONGRESSIONAL UNITS ARE CURRENTLY LOOKING INTO VARIOUS ASPECTS OF USE OF LABORATORY ANIMALS.

THE POSSIBLE EROSION OF PUBLIC SUPPORT FOR OUR POLICIES FOR HUMANE CARE AND USE OF LABORATORY ANIMALS IS A MATTER OF DEEP CONCERN. THE CRITICS OF OUR POLICIES--SOME OF WHOM ARE ATTACKING BIOMEDICAL RESEARCH ON ANIMALS AS NOT ONLY INHUMANE BUT UNNECESSARY--APPEAR TO BE SINCERE AND POLITICALLY SOPHISTICATED. IT IS THEREFORE INCUMBENT ON US TO STRIVE TO BUILD A WIDER CONSENSUS CONCERNING THE POLICY FOR HUMANE CARE AND USE OF LAB ANIMALS.

FOR ITS PART, NIH HAS RECENTLY TAKEN A NUMBER OF ACTIONS AND HAS FUTURE PLANS: NIH HAS COMPLETED SITE VISITS TO TEN INSTITUTIONS RECEIVING SUPPORT FROM NIH TO CONDUCT RESEARCH THAT INVOLVES ANIMALS, ONE EACH IN OUR TEN DISTRICTS, SELECTED AT RANDOM. A REPORT, TO BE RELEASED SOON, SHOULD HELP US STRENGTHEN AND IMPROVE INTERPRETATION OF THE GUIDE AND WILL AFFECT NIH FUTURE POLICY FOR THE CARE AND USE OF ANIMALS. ALTHOUGH THE SITE VISIT TEAMS FOUND NO EVIDENCE THAT ANIMALS WERE BEING UTILIZED INEFFECTIVELY OR TREATED INHUMANELY, THEY DID FIND SOME NON-COMPLIANCE WITH TECHNICALITIES OF NIH GUIDELINES.

NIH IS ALSO IN THE PROCESS OF HAVING ITS GUIDE UPDATED FOR THE FIFTH TIME, UNDER CONTRACT WITH THE NATIONAL ACADEMY OF SCIENCES. THE PROCESS INCLUDED OPEN HEARINGS IN WASHINGTON, SAN FRANCISCO AND CHICAGO IN ORDER TO GAIN COMMENTS FROM THE SCIENTISTS AND THE GENERAL PUBLIC. THE NIH POLICY ON ANIMAL WELFARE IS ALSO BEING REVISED, AND A DRAFT WILL SOON BE ISSUED FOR PUBLIC INPUT. BECAUSE OF ITS SPECIAL CONCERN FOR THE HEALTH AND WELL-BEING OF LABORATORY ANIMALS, NIH'S DIVISION OF RESEARCH RESOURCES (DRR) HAS A SMALL NUMBER OF GRANTS FOR IMPROVEMENT OF LABORATORY ANIMAL FACILITIES, FOR TRAINING SPECIALISTS IN THE LABORATORY ANIMAL FIELD, AND FOR CONTROLLING ANIMAL DISEASES THROUGH A SERIES OF DIAGNOSTIC LABORATORIES. THE LEVEL OF AWARENESS ABOUT LABORATORY ANIMALS IS VERY HIGH ON THE PART OF OUR PEER REVIEW ADVISORS, AND WE CAN EXPECT THEIR CONTINUED VIGILENCE, ESPECIALLY REGARDING DUPLICATION OF EFFORTS INVOLVING ANIMALS, THE PROPOSED USE OF TOO MANY ANIMALS IN A GIVEN PROJECT, OR THE USE OF INAPPROPRIATE ANIMAL MODELS.

NIH ALSO HAS FIRM PLANS TO WIDEN THE PUBLIC FORUM ON THE ISSUE OF ANIMALS INVOLVED IN RESEARCH: IN THE SPRING, WE PLAN TO HOLD A SYMPOSIUM, AT WHICH VARIOUS VIEWS WILL BE HEARD, DESIGNED TO BUILD A BROAD PUBLIC CONSENSUS FOR APPROPRIATE POLICIES FOR THE USE OF ANIMALS IN RESEARCH. STARTING NEXT FALL, NIH WILL BEGIN A SERIES OF EIGHT OR NINE REGIONAL WORKSHOPS DESIGNED TO PROMOTE BETTER UNDERSTANDING AND IMPLEMENTATION OF THE PHS ANIMAL WELFARE POLICY BY INSTITUTIONAL ANIMAL CARE COMMITTEES AND ADMINISTRATORS.

BUT THE FEDERAL GOVERNMENT CANNOT ON ITS OWN ADEQUATELY DEAL WITH THE MOUNTING PRESSURE. IT IS THE RESPONSIBILITY OF THE INSTITUTIONS AND THE INVESTIGATORS TO BECOME MORE ACTIVE IN RESPONDING TO QUESTIONS ABOUT THE NEED FOR ANIMALS IN RESEARCH AND APPROPRIATE SAFEGUARDS. THEY SHOULD BE FAMILIAR WITH THE GUIDELINES AND POLICIES, LOCAL AND NATIONAL, THAT APPLY; THEY SHOULD BE WILLING TO ARTICULATE THE BENEFITS THAT HAVE ACCRUED TO MEDICINE DUE TO ANIMAL PARTICIPATION IN RESEARCH. THOSE WHO ACTUALLY CONDUCT RESEARCH INVOLVING ANIMALS SHOULD BE ABLE TO EXPLAIN CLEARLY TO THE PUBLIC WHY THE ANIMALS ARE ABSOLUTELY NECESSARY IN THE GIVEN EXPERIMENT AND WHY THE EXPERIMENT ITSELF IS IMPORTANT.

ALTHOUGH I HAVE CONCERNED MYSELF IN THIS TALK WITH CURRENT PUBLIC PRESSURES ON VARIOUS ASPECTS OF MEDICAL RESEARCH, I WOULD LIKE TO CONCLUDE WITH A BIT OF HISTORY ON THE SUBJECT. THIS STORY WAS REPEATED BY LEON EISENBERG IN AN ARTICLE IN SCIENCE MAGAZINE--BUT IT WAS A REPRINT OF A LETTER WRITTEN BY LOUIS PASTEUR

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IN 1884 REGARDING VOCIFEROUS COMPLAINTS FROM THE LOCAL CITIZENS ABOUT PROPOSALS TO CREATE DOG KENNELS FOR USE BY THE SCIENTIST. CITIZENS WERE NOT CONCERNED, IN THIS CASE, ABOUT TREATMENT OF THE ANIMALS, RATHER ABOUT THEIR OWN SAFETY AND WELL-BEING. THEY SAID, "THE ANIMALS' CRIES WOULD BE TROUBLESOME; THE EXCREMENTS WOULD BE UNHEALTHY. SINCE M. PASTEUR'S RESEARCH WOULD DEAL NOT ONLY WITH RABIES, BUT ALSO WITH CATTLE PNEUMONIA, ANTHRAX, ERYSIPELAS, CHICKEN POX, ETC., FLIES WOULD BECOME A TERRIBLE CATASTROPHE." PASTEUR WAS WILLING TO FACE THE COMPLAINTS HEAD ON. IN A LETTER TO THE MUNICIPAL COUNSELOR, HE WROTE, "I AM.... GRATEFUL TO YOU FOR ALLOWING ME TO MAKE CLEAR TO THE INHABITANTS....HOW EXAGGERATED ARE THE FEARS ON WHICH SUCH PROTESTS ARE BASED." HE WOULD RETURN TO THE LOCALE SOON, HE WROTE. "I WILL BE READY TO GIVE THE AUTHORS OF THE PROTESTS ALL DESIRED INFORMATION, WHICH, I HOPE, WILL DIMINISH THEIR FEARS. IF MY OWN WORDS ARE NOT SUFFICIENT, I WILL SHOW THE IMPOSSIBILITY OF ANY DANGER WHATSOEVER.... FROM THE EXPERIMENTS WHICH I INTEND TO PERFORM. YOU ARE, SIR, PERFECTLY RIGHT TO CHARACTERIZE THE DANGERS WHICH I WOULD PROVIDE AS ILLUSORY AND AM VERY GRATEFUL TO YOU FOR TRYING TO CALM DOWN ALL THIS TURMOIL. SINCERELY YOURS, PASTEUR."

THE PUBLIC PRESSURE REGARDING PASTEUR'S WORK IS REMINISCENT OF GENERAL PUBLIC REACTION TO DNA RECOMBINANT WORK. I MIGHT POINT OUT THAT PASTEUR'S WORK WENT FORWARD, AS HAS DNA RECOMBINANT WORK, ALBEIT SURROUNDED BY FAR LESS ADMINISTRATIVE ACTIVITY.

INTRODUCTORY REMARKS*

by

James B. Wyngaarden, M.D.**

Thank you very much. Let me add my words of welcome to all of you in this Public Forum. Dr. Lipsett spoke on behalf of the National Institute of Child Health and Human Development. I would like to extend a welcome on behalf of the entire NIH community.

This is a significant conference. It is worth looking back to the origins of the field in which you are interested and in which so many of us have been working. As you know, the concept of inborn errors was originated in 1908 by Sir Archibald Garrod. It took forty years before that concept was confirmed biochemically when Gibson in 1948 demonstrated an absence of NADH dependent methemoglobin reductase in recessive methemoglobinemia. We are now 35 years past that event, and the progress during this time has been remarkable indeed. In fact, there are now about 300 disorders in which the precise biochemical defect has been defined, neglecting the extensive polymorphism of some of these. The last catalog that Victor McKusick published in 1982 lists 934 autosomal dominant conditions, 588 autosomal recessive conditions, and 118 x-linked conditions for which loci are well-established. There is an equal number for which loci have not yet been formally established but which are presumed to exist on sound evidence, giving us at least 3368 discrete inherited diseases defined so far.

We have moved far past the descriptive phase, of course. Extensive heterogeneity is now known to exist for many of these conditions. Gene mapping is now well upon us and over 350 specific genes have been mapped to a precise chromosome, in most of these to a specific location on that chromosome. We have also moved far past mapping, and precise molecular defects have been defined in many conditions at the level of the genes. Specific nucleotide replacement or deletion or insertion in now well-defined for a substantial number of these. I thought it might be interesting to mention just one of these conditions, thalassemia, to which DNA recombinant research has contributed in a special way. In that disorder we have the following precise defects already defined: single base changes in a promoter, premature chain termination mutations at two sites, frameshift mutation at five sites, splice junction mutations at four sites, intron mutations in three positions, and exon mutations affecting RNA processing at two positions. Others will follow very shortly, in fact they already have in The Lesch-Nyhan syndrome where there are five separate mutations now precisely defined: citrillinemia is another example.

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* Presented at the NICHD Public Forum on Gene Therapy on November 21, 1983, in Masur Auditorium, Bethesda, Maryland.

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The study of inborn errors has made enormous contributions to this science, generally in leading to chemical identification of a number of new storage substances, in providing new insights into the biochemical and enzymatic nature of disorders, new insights into the processing and storage of biological materials, identification of new enzymes, identification of new defects of these enzymes in specific disorders, and new approaches to therapy ultimate as enzyme replacement, perhaps shortly gene replacement. The topic raises high emotions, apprehensions, exaggerated expectations and exaggerated fears. A conference such as this can do much to provide a realistic and dispassionate appraisal of the state of the science and future directions, including its ethical and public policy implications.

We look forward to very rapid progress in the near future. The power of these new genetic tools, these new techniques, is awesome. The pace is extremely rapid. It is an excellent idea to pause from time to time to take stock of where we are. You are doing that today.

I wish you well, wish you every success in this very exciting conference.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

I AM DEEPLY GRATEFUL FOR HAVING BEEN ASKED TO PARTICIPATE IN THIS GROUND-BREAKING CEREMONY FOR THE MEDICAL SCIENCES RESEARCH BUILDING OF THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL. IT IS ESPECIALLY MEANINGFUL FOR ME, FOR THIS INSTITUTION IS WHERE I WAS INTRODUCED TO THE ENDLESS CHALLENGES AND REWARDS OF A CAREER IN MEDICINE AND IN BIOMEDICAL RESEARCH.

I AM ALSO GLAD TO BE HERE TO EXPRESS THE ADMIRATION OF THE SCIENTIFIC COMMUNITY FOR WHAT YOU HAVE DONE. THE FACILITY WE SYMBOLICALLY BEGIN TO BUILD TODAY IS POSSIBLE ONLY THROUGH A COURAGEOUS COMMITMENT BY THE SCHOOL OF MEDICINE TO THE SEARCH AT THE FRONTIERS OF THE BIOLOGICAL SCIENCES.

THE SURGE OF DISCOVERY THAT HAS TAKEN PLACE IN THE BIOSCIENCES IN LESS THAN A GENERATION IS WITHOUT PRECEDENT AND IS GATHERING STRENGTH. MANY OF YOU LIKELY HAVE SEEN THE NOVEMBER 18 ISSUE OF SCIENCE MAGAZINE IN WHICH A COLLECTION OF FUNDAMENTAL RESEARCH PAPERS IS PUBLISHED UNDER THE GENERAL HEADING OF "THE REVOLUTION IN BIOLOGY." IN THE LEAD ARTICLE TITLED "BIOLOGICAL FRONTIERS," FREDERICK R. BLATTNER ASSERTED THAT "PHILOSOPHERS AND HISTORIANS OF SCIENCE WILL PROBABLY REGARD THE CURRENT PERIOD AS A TIME OF EXPLOSIVE ADVANCE AND REFINEMENT OF INFORMATION RATHER THAN A TRUE REVOLUTION. IT HAS NOT BEEN NECESSARY, AS WAS THE CASE WITH QUANTUM THEORY OR RELATIVITY, TO OVERTURN MAJOR PARADIGMS OF ACCEPTED THOUGHT; RATHER, AN ENORMOUS INCREASE IN THE POWER OF EXPERIMENTAL TECHNIQUES IS NOW PRODUCING ANSWERS TO COMPLEX, LONG-STANDING BIOLOGICAL QUESTIONS."[1]

WHETHER TERMED AS AN EXPLOSION OR A REVOLUTION, IT IS AN EXCITING TIME INDEED. I FEEL FORTUNATE AS I AM SURE YOU DO TO BE AN ACTIVE PARTICIPANT IN THE ADVANCES BEING MADE BEYOND THE OUTER LIMITS OF THE KNOWN. SUCH PARTICIPATION, BY THE WAY, IS NOT THE PRIVILEGE SOLELY OF THE LABORATORY SCIENTIST. I WILL SPEAK OF THIS LATER.

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*Groundbreaking Ceremonies, Medical Sciences Research Building, University of Michigan, November 22, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

SOME WEEKS AGO, DEAN NIEDERHUBER SENT ME BACKGROUND MATERIAL ON THIS NEW FACILITY IN WHICH IS OUTLINED THE PURPOSES IT WILL FULFILL IN THE OVERALL DEPLOYMENT OF BASIC SCIENCE AND CLINICAL RESEARCH RESOURCES AT THIS INSTITUTION. THE BRIEF PAPER SUMMARIZED THE CONSIDERATIONS OUT OF WHICH THE DECISION WAS MADE TO PROCEED WITH THE PROJECT AND THE BOLD, INNOVATIVE FUNDING PLAN REQUIRED FOR ITS ACCOMPLISHMENT. I FOUND THE BACKGROUND PARAGRAPHS RICH IN OVERTONES SUGGESTIVE OF THE DIFFICULT FINANCIAL ISSUES NOW CONFRONTING MEDICAL SCHOOLS AND ACADEMIC MEDICAL CENTERS ACROSS THE NATION.

THE DEFICIT OF ADEQUATE AND SUITABLE RESEARCH LABORATORY SPACE IS WIDESPREAD. ALTHOUGH THERE IS A DEARTH OF GOOD INFORMATION ON THE ACTUAL REQUIREMENTS, IT IS CLEAR THAT THERE IS A SERIOUS NEED IN MANY INSTITUTIONS TO REPLACE OUTMODED FACILITIES, TO RELIEVE OVERCROWDING, AND TO ACCOMMODATE CHANGING RESEARCH REQUIREMENTS INCLUDING, FOR EXAMPLE, FACILITIES FOR DEALING WITH TOXIC WASTES AND FOR BETTER HOUSING OF LABORATORY ANIMALS.

AND THIS IS HAPPENING AT A TIME WHEN INSTITUTIONS ARE DEALING WITH OVERPOWERING FISCAL PROBLEMS. FEDERAL SUBSIDIES FOR SUCH CONSTRUCTION ENDED IN 1969, EXCEPT FOR CERTAIN LIMITED PROGRAMS OF THE NATIONAL CANCER INSTITUTE AND THE NATIONAL EYE INSTITUTE. MANY OF THE FACILITIES THAT BENEFITED FROM THE HEALTH RESEARCH FACILITIES PROGRAM OF THE NATIONAL INSTITUTES OF HEALTH ARE MORE THAN 20 YEARS OLD.

AGAINST THIS SOMBER BACKGROUND, THE INITIATIVE YOU HAVE TAKEN STANDS OUT IN BRIGHT PERSPECTIVE. THE RESOURCES FOR THIS PROJECT ARE BEING GENERATED BY WHAT YOU HAVE CALLED "A CREATIVE FUNDING PLAN," AND INDEED IT IS. THOSE WORDS STAND AS A REMINDER THAT CREATIVE ACTIVITY IN THE RESEARCH ENTERPRISE IS NOT CONFINED TO THE SCIENTIST AT THE BENCH OR BEDSIDE. THE SUPPORT OF SCIENCE REQUIRES A DIFFERENT DIMENSION OF CREATIVITY--A CREATIVE LEADERSHIP THAT IS COMMITTED TO CONSTRUCTING AND MAINTAINING AN ENVIRONMENT IN WHICH ALL PARTICIPANTS CAN BE CREATIVE. SUCH LEADERSHIP REQUIRES AN UNDERSTANDING OF THE NATURE OF SCIENCE AND A WILLINGNESS TO RISK ITS UNCERTAINTIES.

LEWIS THOMAS ONCE NOTED "IT IS HARD TO PREDICT HOW SCIENCE IS GOING TO TURN OUT, AND IF IT IS REALLY GOOD SCIENCE, IT IS IMPOSSIBLE TO PREDICT. THIS IS THE NATURE OF THE ENTERPRISE."[2]

AT MOST GROUNDBREAKING CEREMONIES, IT IS POSSIBLE TO BE REASONABLY SPECIFIC ABOUT WHAT WILL BE HAPPENING IN THE PROJECTED STRUCTURE. IN THE CASE OF RESEARCH FACILITIES LIKE THIS ONE, HOWEVER, ANY MARKED DEGREE OF SUCH SPECIFICITY IS BOTH IMPOSSIBLE AND UNDESIRABLE. WE CAN BE CONFIDENT, HOWEVER, THAT THIS FACILITY WILL MAKE POSSIBLE THE EXPANSION OF VITAL KNOWLEDGE. IN

TIME THE SCIENTISTS WHO WORK HERE WILL BE RECOGNIZED IN DIFFERENT WAYS FOR THEIR SCIENTIFIC CREATIVITY. IT IS APPROPRIATE THAT TODAY WE RECOGNIZE THE COURAGE AND CREATIVITY REPRESENTED BY THE PLANNING AND FUNDING OF THIS SCIENTIFIC RESOURCE AND THE LEADERSHIP EXERCISED BY THE DEANS, THE DEPARTMENT CHAIRMEN, THE FACULTY, THE REGENTS AND ALL WHO PARTICIPATED IN BRINGING THIS PLAN INTO BEING.

SOME YEARS AGO IN HIS BOOK ON "THE POLITICS OF PURE SCIENCE," DAN GREENBERG MADE AN OBSERVATION THAT STARKLY SUGGESTS THE CHALLENGE TO CREATIVE LEADERSHIP IN SCIENCE. HE NOTED "BEGINNING ABOUT THE SECOND DECADE OF THIS CENTURY, THE FOLKLORE OF SCIENTIFIC INDEPENDENCE, ADMIRABLE AND INSPIRING AS IT MIGHT BE, WAS RAPIDLY BEING ERODED BY RAW ECONOMICS. NATURE NO LONGER HAD MUCH TO REVEAL TO THE DILETTANTE OR THE BAREHANDED INVESTIGATOR."[3]

WITH TODAY'S CEREMONY, WE INITIATE THE CONSTRUCTION OF A TEMPLE OF SCIENCE TO BE PLACED IN THE HANDS OF MANY INVESTIGATORS WHO HERE WILL BE ENABLED TO PROBE EVEN MORE DEEPLY INTO THE UNKNOWN.

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THE FEDERAL-ACADEMIC PARTNERSHIP IN BIOMEDICAL RESEARCH*

by

JAMES B. WYNGAARDEN, M.D.**

SINCE THE 1940s, THE PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH HAVE CONSTITUTED A PRIME EXPRESSION OF FEDERAL POLICY ON BIOMEDICAL RESEARCH IN THE UNITED STATES. THE ESSENCE OF THAT POLICY IS THE ESTABLISHMENT AND NURTURE OF A FEDERAL-ACADEMIC PARTNERSHIP. FROM THE BEGINNING, THAT POLICY HAS ENCOURAGED DIVERSITY AND EXCELLENCE IN HEALTH RESEARCH; FURTHER, IT HAS RELIED ON THE SCIENTIFIC COMMUNITY ITSELF TO IDENTIFY THROUGH A COMPETITIVE PEER REVIEW PROCESS THE IDEAS AND INVESTIGATORS MOST WORTHY OF SUPPORT. IN THIS WAY, PUBLIC FUNDS INVESTED IN BIOMEDICAL RESEARCH HAVE SUPPORTED THE MOST CREATIVE IDEAS AND ENERGIES IN THE AMERICAN HEALTH RESEARCH COMMUNITY--A WEALTH OF IDEAS WHOSE RANGE HAS FAR EXCEEDED THOSE THAT COULD HAVE BEEN GENERATED BY ANY SINGLE COMMITTEE, BOARD, COUNCIL, OR LABORATORY.

IN LESS THAN FOUR YEARS, THE NATIONAL INSTITUTES OF HEALTH WILL CELEBRATE ITS 100TH ANNIVERSARY, COMMEMORATING ITS ESTABLISHMENT AS A ONE-ROOM LABORATORY AT THE MARINE HOSPITAL ON STATEN ISLAND IN 1887. FOR ALMOST 60 YEARS, IT WAS A RELATIVELY SMALL GOVERNMENT LABORATORY CARRYING OUT MOST OF ITS RESEARCH IN-HOUSE. IN SPITE OF ITS LIMITED RESOURCES, THE EARLY ACCOMPLISHMENTS OF THE NIH WERE SUBSTANTIAL. THE STAFF OF THE NIH INCLUDED SOME OF THE GIANTS IN BIOMEDICAL RESEARCH OF THE TIME.

BUT THE NIH AS WE KNOW IT TODAY HAD ITS BEGINNINGS DURING WORLD WAR II. IT WAS DURING THE WAR THAT LEADERS IN GOVERNMENT CAME TO A FULL RECOGNITION OF THE VALUE AND POTENTIAL OF BIOMEDICAL RESEARCH. THEY HAD SEEN THE APPLICATION OF ITS FRUITS TO THE NEEDS OF THE MILITARY. SUCH RAVAGING DISEASES AS YELLOW FEVER, DYSENTERY, TYPHUS, TETANUS, PNEUMONIA, AND MENINGITIS WERE ALL BUT CONTROLLED BY PENICILLIN, THE SULFA DRUGS, NEW INSECTICIDES, BETTER VACCINES, AND IMPROVED HYGIENIC MEASURES.

IN LATE 1944 WHEN PRESIDENT ROOSEVELT BEGAN TO THINK OF THE TRANSITION TO PEACETIME, HE PARADOXICALLY CALLED FOR ANOTHER WAR--BUT THIS WAS TO BE THE WAR OF SCIENCE AGAINST DISEASE.

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*Lecture at the University of Michigan, Ann Arbor, November 22, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

HE WROTE HIS PRINCIPAL SCIENCE ADVISOR VANNEVAR BUSH IN NOVEMBER 1944, POSING A SERIES OF QUESTIONS HAVING DIRECT RELEVANCE TO THE FUTURE OF BIOMEDICAL RESEARCH AND SIGNIFICANTLY TO THE FEDERAL-ACADEMIC PARTNERSHIP. HE ASKED FOR SUGGESTIONS AS TO HOW A PROGRAM MIGHT BE ORGANIZED FOR CONTINUING RESEARCH IN MEDICINE AND THE RELATED SCIENCES. HE ALSO ASKED WHAT THE GOVERNMENT COULD DO THEN AND IN THE FUTURE TO AID RESEARCH ACTIVITIES BY PUBLIC AND PRIVATE ORGANIZATIONS.

IN RESPONSE, VANNEVAR BUSH SUBMITTED A LANDMARK REPORT ON THE PROGRAM FOR POSTWAR SCIENTIFIC RESEARCH TITLED "SCIENCE--THE ENDLESS FRONTIER." THE ESSENCE OF THE REPORT AS IT PERTAINS TO MEDICINE IS CAPTURED IN ONE SENTENCE. DR. BUSH WROTE, "IT IS CLEAR THAT IF WE ARE TO MAINTAIN THE PROGRESS IN MEDICINE WHICH HAS MARKED THE LAST 25 YEARS, THE GOVERNMENT SHOULD EXTEND FINANCIAL SUPPORT TO BASIC MEDICAL RESEARCH IN THE MEDICAL SCHOOLS AND IN THE UNIVERSITIES THROUGH GRANTS BOTH FOR RESEARCH AND FOR FELLOWSHIPS."[1]

HE WAS CALLING FOR A CONTINUATION OF A JOINT FEDERAL-ACADEMIC EFFORT THAT HAD BEEN CONSIDERED AN EMERGENCY MEASURE. DURING THE WAR, THE COMMITTEE ON MEDICAL RESEARCH HAD EXECUTED ABOUT 500 CONTRACTS FOR MEDICAL RESEARCH AT 120 DIFFERENT INSTITUTIONS. OVER 95 PERCENT OF THESE CONTRACTS WERE WITH UNIVERSITIES OR TEACHING HOSPITALS. WITH DEMOBILIZATION, THE NATIONAL COMMITTEE WENT OUT OF BUSINESS BUT INSTEAD OF TERMINATING THE ONGOING GRANTS AND CONTRACTS FOR RESEARCH, THEY WERE TURNED OVER TO THE TINY NATIONAL INSTITUTE OF HEALTH FOR CONTINUATION.

THE CONGRESS AND THE ADMINISTRATION ALMOST AT ONCE BEGAN TO ADD TO THIS INITIAL NEST EGG OF SPONSORED RESEARCH. IN THE INTERVENING YEARS, THE TOTAL OF NIH GRANTS AND CONTRACTS, INITIALLY LESS THAN A MILLION DOLLARS, GREW BY A FACTOR OF MORE THAN 3,000 TO THE 1983 LEVEL OF BETTER THAN THREE BILLION DOLLARS.

AND ALTHOUGH DURING THE SAME PERIOD THE INTRAMURAL RESEARCH PROGRAM AT THE NIH GREW UNTIL IT CONSTITUTES THE WORLD'S LARGEST BIOMEDICAL RESEARCH LABORATORY, THE EARLY EMPHASIS ON THE PARTNERSHIP PARTICULARLY WITH ACADEMIA HAS BEEN MAINTAINED. AT THE PRESENT TIME, APPROXIMATELY 80 PERCENT OF OUR BUDGET IS DEVOTED TO THE SUPPORT OF RESEARCH IN NONFEDERAL LABORATORIES THROUGHOUT THE NATION.

THE SUCCESSION OF LAWS THAT ESTABLISHED AND MOLDED THE NIH WERE WISE, VISIONARY, AND ENORMOUSLY BENEFICIAL. BUT AS FARSIGHTED AND WISE AS THE ENABLING STATUTES HAVE GENERALLY PROVED TO BE, THE DEVELOPMENT AND MATURITY OF THE NIH RESULTED FROM SURE HANDED AND ENLIGHTENED ADMINISTRATION OF THE MANDATES

ACCOMPANIED BY A TOLERANT CONFIDENCE ON THE PART OF THE CONGRESS THAT ITS INTENTION WOULD BE HONORED.

IT WAS FORTUNATE THAT DURING THE PERIOD OF ITS EXPLOSIVE GROWTH FROM 1955 TO THE LATE SIXTIES, THE NIH WAS DIRECTED BY AN UNUSUALLY ABLE AND STRONG LEADER--JAMES A. SHANNON. JIM SHANNON INSISTED THAT THE CONGRESSIONAL MANDATE TO CONDUCT RESEARCH IN CANCER, HEART DISEASE, AND ARTHRITIS, FOR EXAMPLE, BE INTERPRETED BROADLY. HE REALIZED THAT THE SCIENTIFIC BASE WAS NOT SUFFICIENT TO PERMIT A FRONTAL ASSAULT ON THE DISEASES THEMSELVES. HE SET ABOUT TO BUILD THE RESEARCH CAPABILITY OF THIS COUNTRY THROUGH THE INTRAMURAL PROGRAM AT BETHESDA AND THROUGH A SUBSTANTIAL EXPANSION OF THE MECHANISMS OF GRANTS IN AID TO INSTITUTIONS.

COROLLARY OBJECTIVES INCLUDED THE STRENGTHENING OF THE INSTITUTIONS IN WHICH BIOMEDICAL RESEARCH WOULD BE DONE AND THE DEVELOPMENT OF TRAINING MECHANISMS THAT WOULD ENSURE A CONTINUING SUPPLY OF COMPETENT SCIENTISTS DRAWN FROM THE BEST AND BRIGHTEST YOUNG MINDS IN THE UNIVERSITIES. DURING THIS GROWTH PERIOD, HILL BURTON MONEY WAS AVAILABLE FOR CLINICAL FACILITIES, AND NIH CONSTRUCTION FUNDS WERE ALSO AVAILABLE FOR RESEARCH FACILITIES. THROUGH THESE FUNDING MECHANISMS, ACADEMIC MEDICAL CENTERS WERE GREATLY STRENGTHENED.

IN 1983, THE FEDERAL GOVERNMENT CONTRIBUTED ABOUT 53 PERCENT OF THE SUPPORT FROM ALL SOURCES FOR HEALTH-RELATED RESEARCH AND DEVELOPMENT IN THIS COUNTRY. THE NIH BUDGET ACCOUNTS FOR ALMOST 70 PERCENT OF THE TOTAL FEDERAL INVESTMENT, AND ABOUT 60 PERCENT OF OUR EXTRAMURAL FUNDS GO TO ACADEMIC INSTITUTIONS.

FOR DECADES THE MAIN NIH MECHANISM OF RESEARCH SUPPORT HAS BEEN INDIVIDUAL PROJECT GRANTS FOR STUDIES PROPOSED BY NONGOVERNMENT SCIENTISTS. JUST OVER ONE-HALF OF THE NIH BUDGET CURRENTLY IS USED FOR THE SUPPORT OF SUCH INVESTIGATOR-INITIATED PROJECTS.

WITHOUT AN APPRECIATION OF THE SOCIOLOGY OF SCIENCE, ONE MIGHT QUESTION THE WISDOM OF MAKING THE INVESTIGATOR-INITIATED GRANT PROJECT THE KEYSTONE OF A NATIONAL RESEARCH EFFORT. IN USING THIS MECHANISM, WE ARE UTTERLY DEPENDENT UPON THE VOLUNTARY SUBMISSION BY INDIVIDUAL SCIENTISTS OF NEW RESEARCH IDEAS. IN ONE SENSE, IT IS THE FREE ENTERPRISE SYSTEM TAKEN TO THE EXTREME. THE NIH HAS LITTLE OR NO CONTROL OVER THE RANGE OR NATURE OF THE IDEAS SUBMITTED TO IT FOR POSSIBLE FUNDING. YET THIS VERY LACK OF CONTROL IS THE SOURCE OF THE AGENCY'S ABILITY TO TAP THE BEST IDEAS OF THE BEST MINDS IN THE NATION.

THE QUESTION MIGHT BE ASKED, "IF THE INVESTIGATOR-INITIATED GRANT IS SO PRODUCTIVE, WHY DOESN'T NIH DEVOTE ALL FUNDS AVAILABLE FOR EXTRAMURAL RESEARCH

TO THAT MECHANISM?" THE ANSWER IS THAT A NUMBER OF VITAL RESEARCH ACTIVITIES REQUIRE OTHER MECHANISMS; FOR EXAMPLE, LARGE CLINICAL TRIALS. USUALLY THESE TRIALS ARE CONDUCTED SIMULTANEOUSLY AT A NUMBER OF CENTERS SPREAD ACROSS THE COUNTRY. TO ASSURE COMPARABILITY AND VALIDITY OF THE FINDINGS COMING FROM THESE VARIOUS SOURCES, IT IS NECESSARY THAT A UNIFORM PROTOCOL BE RIGIDLY FOLLOWED AT EACH OF THE CENTERS. IN THIS INSTANCE, VARIATIONS FROM THE AGREED UPON RESEARCH PLAN WOULD BE DESTRUCTIVE. SO THE USUAL MECHANISM FOR THE SUPPORT OF CLINICAL TRIALS IS A CONTRACT. SPECIALIZED AND COMPREHENSIVE CENTERS REPRESENT ANOTHER MECHANISM FOR ACCOMPLISHING NIH'S PURPOSES. SUCH CENTERS SUPPORT RESEARCH ON THE CAUSES, PREVENTION, AND TREATMENT OF SPECIFIC DISEASES AND DEMONSTRATION OF NEW METHODS OF TREATMENT.

SUBSTANTIAL FUNDS ARE ALSO DEVOTED TO RESEARCH TRAINING. BECAUSE OF THE CRUCIAL RELATIONSHIP OF TRAINING TO THE FUTURE OF BIOMEDICAL RESEARCH, WE CONSIDER THIS ASPECT OF OUR PROGRAM TO BE OF THE HIGHEST IMPORTANCE.

WHILE, AS I HAVE SAID, THE NIH IS ESSENTIALLY NONDIRECTIVE WITH REGARD TO ITS EXTRAMURAL PROGRAMS, THERE ARE OCCASIONS WHEN WE ATTEMPT TO STIMULATE THE INTEREST OF INVESTIGATORS IN CERTAIN AREAS OF RESEARCH. CURRENTLY, FOR EXAMPLE, WE HAVE ISSUED FORMAL REQUESTS FOR APPLICATIONS ON SUBJECTS RELATED TO ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS). MUCH OF THE IMMUNOLOGICAL RESEARCH THAT WE HAVE SUPPORTED THROUGH THE PAST YEARS HAS A DIRECT BEARING ON THIS DISTURBING NEW PROBLEM AND FORMS AN IMPORTANT BASE FOR FURTHER STUDIES, BUT THERE IS AN URGENT NEED TO FOCUS ON THE PARTICULAR MANIFESTATIONS OF THIS BREAKDOWN OF THE IMMUNE SYSTEM ASSOCIATED WITH AIDS. INTENSIVE EFFORT IS BEING DEVOTED TO THE PROBLEM OF IDENTIFYING THE CAUSATIVE AGENT OF AIDS AND THE POSSIBLE MEANS OF ITS TRANSMISSION, AND WE HAVE CALLED UPON THE RESEARCH COMMUNITY TO FOCUS ON THE PROBLEMS AND TO SUBMIT NEW IDEAS FOR RESEARCH.

WITHIN THE LAST HALF-CENTURY, THE AMERICAN PUBLIC HAS A NEW APPRECIATION OF THE IMPORTANCE OF RESEARCH. THAT PUBLIC CONFIDENCE AND LEVEL OF EXPECTATION HAS DEVELOPED BECAUSE GREAT PROGRESS IN EXPANDING THE BORDERS OF FUNDAMENTAL KNOWLEDGE HAS MADE IT POSSIBLE TO PROCEED TO THE DEVELOPMENT OF POWERFUL MEASURES FOR THE PREVENTION AND TREATMENT OF DISEASES. BUT THE BASE OF KNOWLEDGE MUST COME FIRST AND IT IS FOR THIS REASON THAT THE NIH CONTINUES ITS POLICY OF COMMITTING A LARGE SHARE OF ITS BUDGET TO BASIC STUDIES. AN ESTIMATED 90 PERCENT OF THE BASIC BIOMEDICAL RESEARCH IN THIS COUNTRY IS SUPPORTED OR CONDUCTED BY THE NIH.

BECAUSE PUBLIC AND PRIVATE FUNDS FOR RESEARCH ARE NOT UNLIMITED, IT IS INCUMBENT ON ALL OF US TO ASSURE THAT SUPPORT IS GIVEN TO WORK OF THE HIGHEST QUALITY.

PEER REVIEW FOR QUALITY ASSURANCE IS AT THE VERY HEART OF THE NIH SYSTEM. IN CARRYING OUT ITS MISSION, OUR AGENCY IS NOT ONLY DEPENDENT UPON THE SCIENTIFIC COMMUNITY FOR THE INITIATION AND PROPOSAL OF RESEARCH SUBJECTS; IT ALSO DRAWS HEAVILY UPON THE NATION'S SCIENTIFIC COMMUNITY FOR THE EXPERTISE NEEDED IN MAKING THE CRITICAL JUDGMENTS AMONG COMPETING PROPOSALS.

IN THIS PROCESS, WE RELY ALMOST EXCLUSIVELY ON MEMBERS OF THE NONFEDERAL SCIENTIFIC COMMUNITY. INVESTIGATORS IN THE MANY DISCIPLINES OF BIOMEDICAL SCIENCE ARE APPOINTED TO INITIAL REVIEW COMMITTEES CALLED STUDY SECTIONS. THE STUDY SECTIONS ARE ORGANIZED ALONG TRADITIONAL DISCIPLINARY LINES; FOR EXAMPLE, HEMATOLOGY, CELL BIOLOGY, PHARMACOLOGY, AND SO FORTH. SIXTY-FOUR COMMITTEES OF THIS TYPE MEET THREE TIMES EACH YEAR TO REVIEW GRANT APPLICATIONS ASSIGNED TO THEM. MEMBERS OF THE STUDY SECTIONS ARE CAREFULLY SELECTED ON THE BASIS OF THEIR OWN SCIENTIFIC PERFORMANCE AND ARE APPOINTED FOR FOUR-YEAR TERMS.

THE STUDY SECTIONS ASSESS THE SCIENTIFIC MERIT AND TECHNICAL FEASIBILITY OF SOME FIFTEEN TO TWENTY THOUSAND GRANT APPLICATIONS EACH YEAR AND ASSIGN TO EACH A RATING OR A PRIORITY SCORE. IN LATER CONSIDERATIONS, THAT SCORE BECOMES THE SINGLE MOST IMPORTANT FACTOR WHEN THE FINAL DECISION IS MADE TO FUND OR NOT TO FUND.

FOLLOWING REVIEW BY THE STUDY SECTIONS, THE APPLICATIONS ARE THEN ASSIGNED FOR CONSIDERATION BY ONE OF THE ELEVEN INSTITUTES OF THE NATIONAL INSTITUTES OF HEALTH. AT THE INSTITUTE, A SECOND REVIEW IS CONDUCTED BY THE NATIONAL ADVISORY COUNCIL OF THE PROSPECTIVE FUNDING INSTITUTE. THESE COUNCILS INCLUDE IN THEIR MEMBERSHIP NOT ONLY SCIENTISTS BUT PUBLIC MEMBERS AS WELL. IN THE COUNCILS, ADDITIONAL JUDGMENTS ARE MADE ON THE BASIS OF THE PROGRAM CONCERNS OF THE INSTITUTE. BY LAW NO GRANT MAY BE AWARDED THAT HAS NOT BEEN RECOMMENDED FOR AWARD BY THE NATIONAL ADVISORY COUNCIL OF THE FUNDING INSTITUTE.

CURRENTLY, MANY STRONG, POTENTIALLY PRODUCTIVE AND VALUABLE RESEARCH PROJECTS CANNOT BE FUNDED AND EXCELLENT ESTABLISHED INVESTIGATORS AS WELL AS WELL-QUALIFIED NEWCOMERS ARE BEING DENIED SUPPORT BECAUSE OF THE STRINGENCY OF THE BUDGET. IT IS ONLY NATURAL AT SUCH A TIME THAT THE MECHANISM BY WHICH JUDGMENTS ARE MADE WOULD COME UNDER EXTERNAL PRESSURE. SOME SCIENTISTS HAVE ATTACKED THE FUNDAMENTAL INTEGRITY AND EQUITY OF THE PEER REVIEW SYSTEM. IT IS A HUMAN SYSTEM AND NO ONE WOULD CONTEND THAT ITS JUDGMENTS ARE FLAWLESS. YET IT HAS OPERATED WITH VERY LITTLE CRITICISM FOR 30 YEARS AND WE CONTINUE TO HAVE THE STRONGEST CONFIDENCE IN ITS OVERALL PERFORMANCE.

FOR THOSE OF US WHO IN ONE WAY OR ANOTHER HAVE HAD CONTACT WITH THE NIH OVER A PERIOD OF TIME, THESE SIGNS OF STRESS SHOULD COME AS NO SURPRISE. THE AGENCY WENT THROUGH A SPECTACULAR PERIOD OF GROWTH IN THE MID-FIFTIES AND EARLY

SIXTIES. IT WAS A TIME WHEN YEAR-TO-YEAR BUDGET INCREASES AVERAGED AROUND 25 PERCENT. WHAT WAS ENTIRELY FORESEEABLE HAS HAPPENED. ALTHOUGH OUR ANNUAL APPROPRIATION IS NOW WELL OVER FOUR BILLION DOLLARS--TEN TIMES WHAT IT WAS IN 1960--THE INCREASES FOR THE PAST DECADE HAVE BARELY KEPT PACE WITH INFLATION.

BY 1975, THE NIH APPROPRIATION HAD JUST REACHED TWO BILLION DOLLARS, BUT THE POSITIVE SLOPE OF THE GROWTH CURVE WAS FLATTENING NOTICEABLY.

(SLIDE 1)

AS EARLY AS 1974, THE NIH HAD BEGUN ACCOMMODATING TO A RELATIVELY CONSTANT BUDGET BY FUNDING AN INCREASING NUMBER OF EXCELLENT RESEARCH PROPOSALS THROUGH SHIFTING FUNDS FROM AMONG VARIOUS OTHER PROGRAM MECHANISMS.

THERE WAS A CLEAR NEED FOR ARTICULATION OF POLICY FOR GUIDANCE THROUGH THE UNCHARTED FUNDING PLATEAU. IN 1978, UNDER THE LEADERSHIP OF THEN DIRECTOR DONALD FREDRICKSON, ALSO A MICHIGAN GRADUATE, AND SECRETARY JOSEPH CALIFANO, A NATIONAL CONFERENCE ON HEALTH RESEARCH PRINCIPLES WAS HELD IN BETHESDA. ITS PURPOSE WAS TO DRAW OUT IDEAS FROM THE DEPARTMENT'S HEALTH AGENCIES AND THE RESEARCH COMMUNITY AT LARGE FOR A RESEARCH PLAN TO HELP GUIDE IN THE ALLOCATION OF LIMITED RESOURCES. MORE THAN 100 NONFEDERAL SCIENTISTS, MANY OF THEM REPRESENTING MAJOR SEGMENTS OF THE SCIENTIFIC COMMUNITY, PARTICIPATED ACTIVELY IN THE CONFERENCE DISCUSSIONS.

ALL PARTIES TO THE CONFERENCE AGREED ON THE ESSENTIALITY OF THE FEDERAL COMMITMENT TO INSURE A STRONG SCIENCE BASE FOR HEALTH. THEY REPEATEDLY STRESSED THE NEED FOR LONG-TERM STABILITY IN THE FUNDING OF HEALTH RESEARCH AND WARNED THAT PRESENT RESEARCH CAPABILITIES MUST BE SUSTAINED AND ENHANCED TO ASSURE FUTURE HEALTH GAINS.

THESE CONSIDERATIONS STIMULATED THE DEVELOPMENT OF THE SO-CALLED "STABILIZATION STRATEGY" THAT WAS CONCEIVED TO BENEFIT BIOMEDICAL RESEARCH. AS APPLIED TO RESEARCH PROJECT GRANTS, THE MOST IMPORTANT COMPONENT OF THE SCIENCE BASE, A MAJOR GOAL WAS TO MINIMIZE THE YEAR-TO-YEAR FLUCTUATIONS IN THE NUMBERS OF NEW AND COMPETING RENEWAL GRANTS AND THEREBY TO REDUCE THE LIKELIHOOD THAT INVESTIGATORS WOULD FORSAKE RESEARCH CAREERS BECAUSE OF THE APPEARANCE OF UNPREDICTABILITY OF FUNDING OPPORTUNITIES.

AMIDST THE HECTIC GIVE AND TAKE OF THE BUDGET PROCESS WITHIN THE ADMINISTRATION AND THE CONGRESS, THE FIRST STEP TOWARD EFFECTING THE STABILIZATION CONCEPT WAS TO APPLY IT TO RESEARCH PROJECT GRANTS. A GOAL OF FUNDING AT LEAST 5,000 NEW AND COMPETING RENEWAL RESEARCH GRANTS ATOP A BASE OF MORAL COMMITMENTS

COMPRISING APPROXIMATELY 11,000 NONCOMPETING CONTINUATION GRANTS BECAME AN END IN ITSELF--AN END TO BE MET IF NECESSSARY BY REPEATED DOWNWARD NEGOTIATIONS IN DIRECT COSTS FROM THE LEVELS RECOMMENDED BY PEER REVIEWERS, BY PAYMENT OF LESS THAN FULL INDIRECT COSTS, AND BY REDUCTION IN OTHER IMPORTANT PROGRAM ACTIVITIES.

THE PRESENT AND CONTINUED ADHERENCE TO THE ABRIDGED STABILIZATION STRATEGY HAS BECOME A PROBLEM IN THAT IT DOES NOT REFLECT A BROAD VIEW OF THE NEEDS THROUGHOUT BIOMEDICINE, EVEN THOUGH IT DOES MUCH TO PROTECT THE MOST IMPORTANT MECHANISM FOR THE GENERATION OF NEW KNOWLEDGE--THE INVESTIGATOR-INITIATED RESEARCH GRANT. SERIOUS CONCERNS IN THIS REGARD HAVE BEEN ADVANCED BY NIH INSTITUTE DIRECTORS, BY THE NIH DIRECTOR'S ADVISORY COMMITTEE, BY NATIONAL ADVISORY COUNCILS, AND BY OTHER GROUPS REPRESENTATIVE OF THE RESEARCH COMMUNITY OR THE PUBLIC AT LARGE. HOWEVER, A SUPERIOR ALTERNATIVE HAS YET TO BE ARTICULATED, MUCH LESS BECOME ADOPTED AS BROADLY AND FERVENTLY AS HAS THE CURRENT STRATEGY.

WHILE IT IS TRUE THAT NIH HAS SUPPORTED AT LEAST 5,000 NEW AND COMPETING RENEWAL RESEARCH PROJECT GRANTS EACH YEAR SINCE 1980--AND IN 1983 THE TOTAL WAS ABOUT 5,400--IT WOULD BE INCORRECT TO CONTEND THAT MAINTENANCE OF THIS NUMBER PER SE HAS PRODUCED STABILITY FOR THE BIOMEDICAL RESEARCH ENTERPRISE OVERALL. THE FACT THAT WE HAVE FOUND IT NECESSARY TO FUND RESEARCH PROJECT GRANTS AT LEVELS WELL BELOW THOSE RECOMMENDED BY PEER REVIEWERS IS A CHRONIC SOURCE OF CONCERN TO ALL INVOLVED. MOREOVER, REPEATED AND UNPREDICTABLE REDUCTIONS IN THE FRACTION OF TOTAL NIH DOLLARS AVAILABLE FOR ALL OTHER FUNDING MECHANISMS, INCLUDING TRAINING AND RESEARCH CAREER AWARDS, RESEARCH CENTERS AND CONTRACTS, HAS LED TO LESS THAN DESIRABLE LEVELS OF EFFORT IN COMPLEMENTARY AREAS.

NUMEROUS PROPOSALS HAVE BEEN MADE RECENTLY TO STRETCH THE RESEARCH DOLLAR BY LIMITING OR REDUCING THE AMOUNTS PAID ON INDIVIDUAL GRANTS IN ORDER TO FREE FUNDS TO SUPPORT ADDITIONAL AWARDS. THESE PROPOSALS HAVE BEEN CONSIDERED BY THE NIH AND HAVE FOUND TO BE LACKING IN MANY RESPECTS, NOT THE LEAST OF WHICH IS THE IMPLICATION THAT RESEARCH AWARDS REPRESENT A FULL EMPLOYMENT PROGRAM FOR SCIENTISTS. THIS PROPOSAL BRINGS TO MIND THE STATEMENT IN TESTIMONY BY PHILIP HANDLER. HE SAID, "IN SCIENCE THE BEST IS VASTLY MORE IMPORTANT THAN THE NEXT BEST," OR JOHN GARDNER'S QUERY, "CAN WE BE EQUAL AND EXCELLENT, TOO?"

HOWEVER, IN FY 82, THE NIH INSTITUTED A FORMAL POLICY OF AWARDING GRANTS AT AMOUNTS LESS THAN THOSE RECOMMENDED BY THE PEER REVIEW GROUPS AS A WAY OF MAXIMIZING THE NUMBER OF GRANTS THAT COULD BE SUPPORTED WITHIN A GIVEN BUDGET LEVEL.

ALTHOUGH AS DEMONSTRATED BY THE 1982 AND 1983 EXPERIENCE, THIS POLICY HAS PROVIDED SHORT-TERM RELIEF FROM BUDGET STRINGENCIES, IT HOLDS LITTLE PROMISE OF CONTRIBUTING TO LONG-TERM SOLUTIONS. JUST AS THERE ARE LIMITS TO THE AMOUNTS OF RESOURCES THAT CAN BE SHIFTED FROM OTHER PROGRAM MECHANISMS TO SUPPORT THE FUNDING OF PROJECT GRANTS, SO ARE THERE LIMITS TO THE REDUCTIONS THAT CAN BE MADE IN FUNDS AWARDED TO SUPPORT OF AN INDIVIDUAL RESEARCH PROJECT GRANT WITHOUT DEFEATING THE PURPOSES FOR WHICH THOSE FUNDS WERE AWARDED.

DESPITE THE UNTOWARD SIDE EFFECTS OF THE RECENT PARTIAL IMPLEMENTATION OF A STABILIZATION POLICY, THE NIH HAS NO DESIRE TO ABANDON THE CONCEPT AND WE RECOGNIZE THE POSITIVE EFFECT OF EVEN AN INCOMPLETE APPLICATION OF THIS LONG-RANGE PLAN DURING A TIME OF FISCAL STRINGENCY. IT IS OUR CONVICTION THAT THE IMPORTANT NEEDS ADDRESSED BY THE ORIGINAL STABILIZATION STRATEGY REMAIN AND THAT THE ESSENTIAL COMPONENTS OF THE STRATEGY CONTINUE TO BE VITAL AS MEANS FOR ADDRESSING THOSE NEEDS.

WE NEED TO ASSURE ADEQUATE LEVELS OF SUPPORT FOR THE ENTIRE RESEARCH ENTERPRISE IF WE ARE TO PRESERVE THE MOMENTUM OF DISCOVERY. WE BELIEVE THAT THE OPTIMAL LEVEL FOR PROGRESS IS TO BE ABLE TO AWARD 45 TO 50 PERCENT OF APPROVED APPLICATIONS FOR RESEARCH SUPPORT. IN THE CONTEXT OF THE FEDERAL BUDGET, THE SUMS NEEDED ARE NOT LARGE. LAST DECEMBER I EXPRESSED TO THE DIRECTOR'S ADVISORY COMMITTEE MY BELIEF THAT TO ACHIEVE SUCH A GOAL, WE WOULD NEED AN ADDITIONAL THREE TO FOUR HUNDRED MILLION DOLLARS PER YEAR FOR THREE YEARS, WITH STEADY FUNDING FOR NEW AWARDS THEREAFTER. IT IS ENCOURAGING THAT THE INCREASE FOR 1984 APPROACHES THAT PROJECTION.

BUT A PROJECTION BASED ON A 50 PERCENT AWARD RATE, ESSENTIALLY FULL FUNDING OF GRANTS, AND MAINTENANCE OF BALANCE AMONG THE ESSENTIAL MECHANISMS FOR RESEARCH SUPPORT WOULD REQUIRE MUCH LARGER SUMS, PERHAPS A DOUBLING OF THE NIH BUDGET BY 1990 EVEN IF A MODEST RATE OF INFLATION IS ASSUMED.

IN SPEAKING OF THE ESSENTIAL MECHANISMS FOR RESEARCH SUPPORT, I WOULD INCLUDE AT THE MINIMUM ADEQUATE FUNDING FOR CENTERS, FOR CONTRACTS, FOR INTRAMURAL RESEARCH AND FOR TRAINING, AS WELL AS FOR RESEARCH GRANTS. WE CONSIDER FIRST-TIME GRANTEES A HIGHLY IMPORTANT CATEGORY OF INVESTIGATORS WHO MUST BE ADEQUATELY SUPPORTED BY NIH AWARDS. IN 1982, ABOUT 8 PERCENT OF OUR AWARDEES WERE "FIRST-TIMERS"--THIS, BY THE WAY, IS THE LOWEST THAT RATIO HAD BEEN IN A DECADE. IN FY 83, WHEN WE FUNDED 39 PERCENT OF STUDY SECTION APPROVED AWARDS, THIS FIGURE ROSE SOME BUT PRECISE FIGURES ARE NOT YET AVAILABLE.

AT THE OTHER END OF THE GRANTEE SPECTRUM IS THE OUTSTANDING ESTABLISHED INVESTIGATOR FOR WHOM A MECHANISM IS NEEDED FOR PROVIDING LONGER TERM, MORE FLEXIBLE SUPPORT.

ANOTHER MATTER REQUIRING ATTENTION IF THE FEDERAL-ACADEMIC PARTNERSHIP IS TO CONTINUE TO FLOURISH IS THE NEED TO REPLACE OR PURCHASE THE INCREASINGLY SOPHISTICATED INSTRUMENTS REQUIRED FOR TODAY'S RESEARCH. IT IS ESTIMATED THAT 20 MILLION DOLLARS A YEAR FOR FIVE YEARS IS NEEDED FOR THE ACQUISITION OF LARGE-SCALE SHARED INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE THROUGH RESEARCH GRANTS OF SMALLER INSTRUMENTS. THE NIH HAS RECENTLY JOINED AN ONGOING STUDY BY THE NATIONAL SCIENCE FOUNDATION FOR THE PURPOSE OF SECURING A VALID CURRENT ASSESSMENT OF NATIONAL NEED.

EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. I MENTIONED EARLIER AT THE GROUNDBREAKING CEREMONY THAT WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND MORE RECENTLY BY THE NATIONAL EYE INSTITUTE, NIH STOPPED SUPPORTING THE CONSTRUCTION OF FACILITIES AFTER 1969 AND CURRENTLY LACKS LEGAL AUTHORITY TO DO SO. AS A CONSEQUENCE, MANY OF THE FACILITIES BENEFITING FROM THE MAJOR NIH CONSTRUCTION EFFORT--THE HEALTH RESEARCH FACILITIES PROGRAM--ARE MORE THAN 20 YEARS OLD, OR RAPIDLY APPROACHING THAT MARK.

THE COURAGEOUS INITIATIVE THAT THIS INSTITUTION HAS TAKEN STANDS AS AN ILLUSTRATION OF THE NEED AND OF THE ENORMOUS DIFFICULTIES FACED BY INSTITUTIONS IN MEETING THE NEED FOR SUITABLE AND ADEQUATE RESEARCH FACILITIES.

AS IMPORTANT AS BUILDINGS AND INSTRUMENTATION MAY BE, THERE IS ANOTHER CONSIDERATION OF EVEN GREATER MOMENT. THIS SUBJECT IS NECESSARILY A PART OF ANY DISCUSSION OF THE FEDERAL-ACADEMIC PARTNERSHIP. THAT SUBJECT IS RESEARCH TRAINING.

IN OUR VIEW, THE TRAINING AND RESEARCH PROGRAMS ARE SO CLOSELY INTERWOVEN AS TO BE PRACTICALLY INDIVISIBLE. WE BELIEVE THAT TO ASSURE THE CONTINUED SUCCESS OF RESEARCH ACTIVITY, AN ACTIVE RESEARCH MANPOWER DEVELOPMENT PROGRAM MUST BE SUSTAINED FOR SELECT INDIVIDUALS AT ALL STAGES OF INTELLECTUAL AND PROFESSIONAL DEVELOPMENT.

THE BOND BETWEEN TRAINING AND RESEARCH WAS ADDRESSED RECENTLY IN A STATEMENT BY DR. GEORGE KEYWORTH, THE PRESIDENT'S SCIENCE ADVISOR. HE NOTED THAT "AS A GROUP, AMERICAN RESEARCH UNIVERSITIES ARE THE BEST IN THE WORLD, BOTH IN TERMS OF PRODUCING THE NEW KNOWLEDGE THAT STIMULATES TECHNOLOGY AND IN TERMS OF PRODUCING THE PEOPLE WHO DRIVE THE INNOVATIVE PROCESS IN SOCIETY. THAT UNIQUE DUAL FUNCTION," HE SAYS, "EXPLAINS OUR TREMENDOUS EMPHASIS ON UNIVERSITY RESEARCH. NO OTHER RESEARCH INSTITUTIONS--FEDERAL LABORATORIES, NONPROFIT ORGANIZATIONS, OR INDUSTRIAL LABORATORIES--GIVE SO MUCH IN RETURN ON INVESTMENT IN THE LONG TERM. NO OTHER INSTITUTIONS PRODUCE BOTH KNOWLEDGE AND PEOPLE."[2]

(SLIDE 2)

THE INTENSE COMPETITION FOR RESEARCH SUPPORT HAS INCREASINGLY TAKEN ITS TOLL OF THE AMATEUR OR UNDERTRAINED INVESTIGATOR. THE PROFESSIONALIZATION OF RESEARCH ACTIVITY HAS PROGRESSIVELY SELECTED AGAINST THE M.D. SCIENTIST WHO 15 YEARS AGO HAD A MUCH BETTER PROSPECT OF SUCCESS IN RESEARCH APPLICATIONS THAN THE PH.D. APPLICANT. CONCURRENTLY, THERE HAS BEEN A DECREASE IN THE NUMBER OF PHYSICIANS WHO ARE SEEKING RESEARCH TRAINING.

(SLIDE 3)

THE APPLICATION OF SCIENTIFIC ADVANCES TO MAINTAIN GOOD HEALTH AND TO PREVENT AND TREAT DISEASE IS ULTIMATELY THE RESPONSIBILITY OF THE PHYSICIAN. THE TRAINED CLINICAL INVESTIGATOR IS THE CRITICAL LINK BETWEEN THE LABORATORY AND THE HEALTH CARE PROVIDER. IN THE FACE OF THE EXPLOSIVE GROWTH OF BASIC KNOWLEDGE IN THE BIOMEDICAL SCIENCES WHICH HAS OPENED UP VAST OPPORTUNITIES FOR CLINICAL RESEARCH, THE SHORTFALL IN TRAINING OF CLINICAL INVESTIGATORS ASSUMES ADDITIONAL SIGNIFICANCE.

DESPITE THESE NEGATIVE FACTORS AND PARTLY TO COUNTER THEM, THE NIH HAS DEVELOPED SEVERAL PROGRAMS IN ADDITION TO ITS REGULAR RESEARCH TRAINING GRANTS THAT ARE DESIGNED TO ACQUAINT THE PHYSICIAN IN TRAINING WITH THE EXCITEMENT AND POSSIBILITIES OF BIOMEDICAL RESEARCH.

THE NEWEST ADDITION TO THE CAREER DEVELOPMENT PROGRAM, CALLED THE PHYSICIAN-SCIENTIST AWARD, WAS ANNOUNCED LAST JULY. THIS AWARD IS SUPPORTED BY SEVERAL OF THE NIH INSTITUTES. IT IS DESIGNED TO PROVIDE FIVE YEARS OF PHASED SUPERVISED RESEARCH TRAINING, BEGINNING WITH TWO TO THREE YEARS IN A BASIC

SCIENCE LABORATORY. THE AWARD WILL CARRY A SALARY EQUIVALENT TO THAT EARNED BY A MEMBER OF THE INSTITUTION'S HOUSE STAFF WITH EQUIVALENT EXPERIENCE AND AN ADDITIONAL MODEST AWARD TO THE TRAINING INSTITUTION TO COVER RESEARCH COSTS DURING THE TRAINING PROGRAM.

I HAVE SPOKEN OF THE LONG STANDING FEDERAL-ACADEMIC PARTNERSHIP WHICH HAS BEEN SO EFFECTIVE AND MUTUALLY REWARDING. RECENTLY WE HAVE SEEN THE BEGINNINGS OF THE DEVELOPMENT OF PARTNERSHIPS BETWEEN ACADEMIC INSTITUTIONS AND INDUSTRY. THERE HAVE BEEN SUGGESTIONS THAT THE NIH TAKE SOME KIND OF ACTIVE PART IN THE INSTITUTION OF THESE NEW RELATIONSHIPS. WE HAVE NOT DONE SO. WE BELIEVE IT PERFERABLE THAT THE NEW FORMS OF JOINT ENDEAVOR CONTINUE TO EVOLVE AS THEY HAVE BEEN WITH GOVERNMENT PLAYING A FACILITATIVE ROLE. EVEN THOUGH THE AREAS OF COLLABORATION BETWEEN THE UNIVERSITIES AND INDUSTRY HAVE BROADENED SIGNIFICANTLY AND PROMISE TO CONTINUE IN THAT EXPANSION, I BELIEVE IT SAFE TO PREDICT THAT THE GOVERNMENT WILL CONTINUE AS THE PRINCIPAL SOURCE OF FUNDING FOR BASIC RESEARCH.

WITHIN SCIENCE ITSELF, THERE HAS BEEN A GRADUAL CHANGE HAVING PROFOUND IMPLICATIONS. NOBEL LAUREATE ARTHUR KORNBERG RECENTLY CALLED ATTENTION TO THE "CONFLUENCE OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SUBJECTS INTO A SINGLE UNIFIED DISCIPLINE." HE OBSERVED THAT "ANATOMY, PHYSIOLOGY, BIOCHEMISTRY, MICROBIOLOGY, IMMUNOLOGY AND GENETICS HAVE NOW BEEN MERGED AND ARE EXPRESSED IN A COMMON LANGUAGE OF CHEMISTRY."[3]

IT IS IRONIC THAT CONCURRENTLY WITH THIS CONFLUENCE OF THE SCIENTIFIC DISCIPLINES, THERE ARE INCREASING PRESSURES ON THE NIH FOR FRAGMENTATION THROUGH THE CREATION OF NEW ORGANIZATIONAL ENTITIES EACH HAVING A RELATIVELY NARROW FOCUS ON A PARTICULAR SET OF HEALTH PROBLEMS.

SUCH MOVEMENTS GAIN MUCH OF THEIR STRENGTH FROM, AND INDEED ARE AN EXPRESSION OF, THE PUBLIC CONFIDENCE IN THE POWER OF RESEARCH. THE MOVEMENTS ARE ALSO AN UNDERSTANDABLE REACTION BY SEGMENTS OF THE BIOMEDICAL COMMUNITY TO THE FUNDING CRUNCH AND REPRESENT AN EFFORT TO ESTABLISH ALTERED RESEARCH PRIORITIES THROUGH CONGRESSIONAL ACTION.

THE NIH AND THE DEPARTMENT OF HEALTH AND HUMAN SERVICES HAVE OPPOSED LEGISLATION FOR THE CREATION OF NEW INSTITUTES AND FOR THE ESTABLISHMENT IN STATUTE OF FAVORED STATUS FOR SPECIFIC RESEARCH PROGRAMS. OUR OPPOSITION TO THESE PROPOSALS IS BASED NOT ONLY ON THEIR ADVERSE EFFECTS ON ADMINISTRATIVE COSTS AND FLEXIBILITY, BUT ALSO BECAUSE THE COMPARTMENTALIZATION THEY ESTABLISH IS COUNTER TO THE DIRECTION IN WHICH SCIENCE IS MOVING. LAST FRIDAY THE HOUSE PASSED LEGISLATION AUTHORIZING THE CREATION OF TWO NEW INSTITUTES--ONE THE NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL DISEASES AND THE OTHER THE NATIONAL INSTITUTE OF NURSING. AT A TIME WHEN WE CAN CONFIDENTLY PREDICT

UNUSUALLY RAPID MOVEMENT IN SCIENCE AND WE CANNOT PREDICT JUST WHERE THAT PROGRESS WILL OCCUR, WE NEED THE MAXIMUM FLEXIBILITY FOR MARSHALING FINITE RESOURCES FOR SUPPORT OF SCIENCE.

NOTWITHSTANDING OUR CONCERNS ABOUT THE PROLIFERATION OF INSTITUTES, ADAMANT REFUSAL ON THE PART OF THE NIH TO CONSIDER CHANGE IS SHORTSIGHTED. LAST JUNE WE ASKED THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES TO MAKE AN OBJECTIVE STUDY OF THE ORGANIZATIONAL STRUCTURE OF THE NIH AND TO RECOMMEND THE ESTABLISHMENT OF STANDARDS FOR DETERMINING THE NEED FOR ANY SUBSTANTIAL CHANGE IN THE STRUCTURE OF THE AGENCY. WE EXPECT THE STUDY TO BE COMPLETED AND TO HAVE A REPORT FROM THE IOM IN NOVEMBER OF 1984.

OUR PAST HISTORY OF COOPERATION WITH THE NONFEDERAL SCIENTIFIC COMMUNITY IN THE EVOLUTION OF OUR NATION'S GREAT BIOMEDICAL RESEARCH ENTERPRISE GIVES ME CONFIDENCE IN OUR ABILITY TO SOLVE CURRENT PROBLEMS THROUGH WORKING TOGETHER. WHILE WE ALL ENCOURAGE THE INTENSE COMPETITION THAT DRIVES SCIENTIFIC DISCOVERY, WE SHOULD VIEW OURSELVES AS COLLABORATORS IN THE OPERATION OF THE SYSTEM THAT SUPPORTS THE RESEARCH EFFORT. WE ARE VITALLY CONCERNED FOR THE HEALTH AND STABILITY OF THE INSTITUTIONS IN WHICH SO MUCH OF THE ESSENTIAL RESEARCH IS CONDUCTED, JUST AS THEY ARE FOR THE SUCCESS OF THE NIH. THE ENLIGHTENED FEDERAL POLICY ON BIOMEDICAL RESEARCH IN THIS COUNTRY HAS BEEN UNUSUALLY SUCCESSFUL. GOVERNMENT AND THE SCIENTIFIC COMMUNITY HAVE FORMED A STRONG AND HEALTHY PARTNERSHIP BASED ON LONG STANDING PRINCIPLES OF COOPERATION IN THE CAUSE OF SCIENCE AND THE STRENGTH OF THIS PARTNERSHIP WILL SERVE US WELL IN ARRIVING AT MUTUALLY SATISFACTORY AND PRODUCTIVE SOLUTIONS TO THE PROBLEMS WE BOTH FACE. WE SHARE OBJECTIVES OF THE HIGHEST MERIT; NAMELY, THE CONQUEST OF DISEASE AND BETTER HEALTH FOR ALL.

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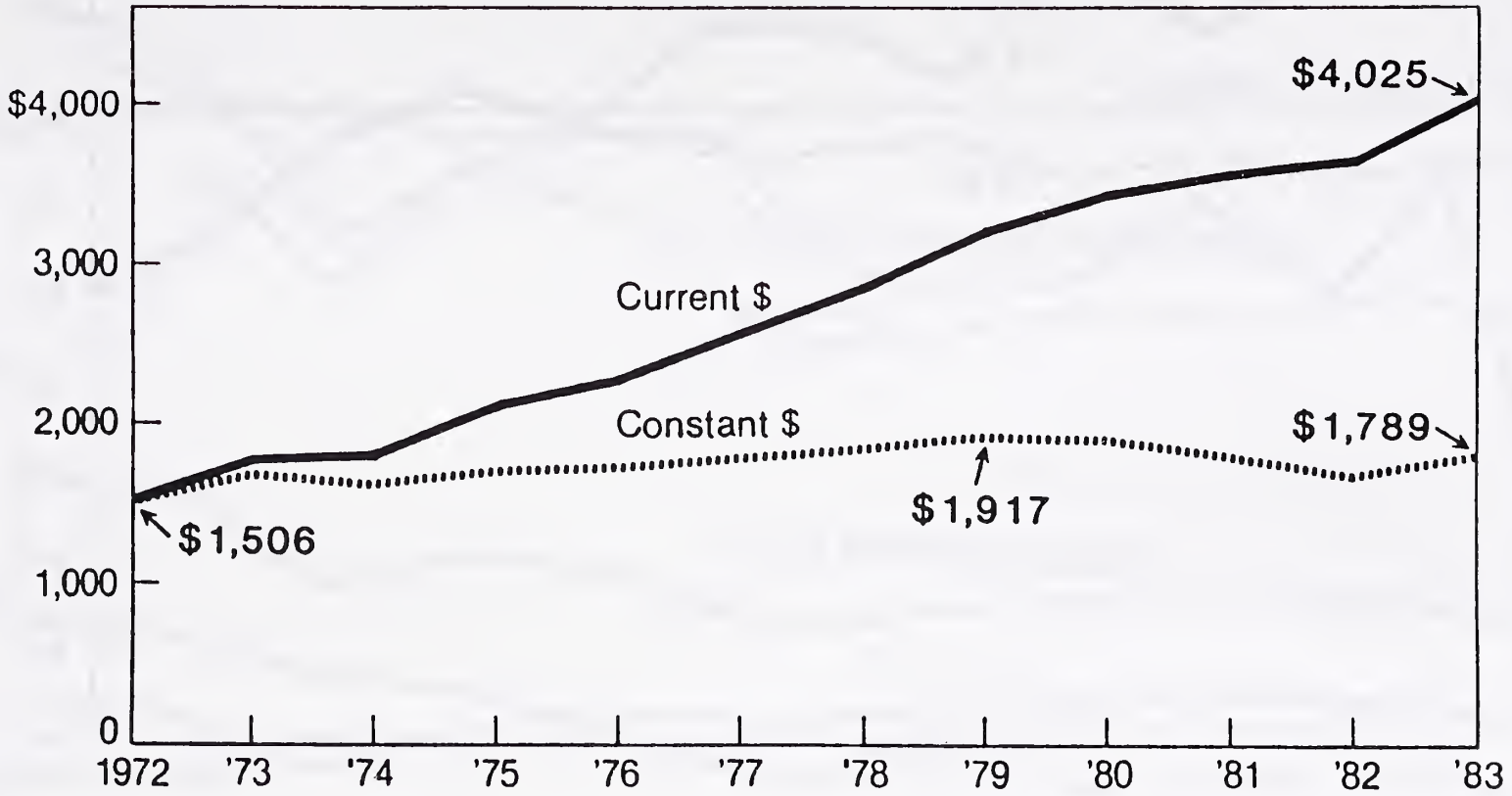
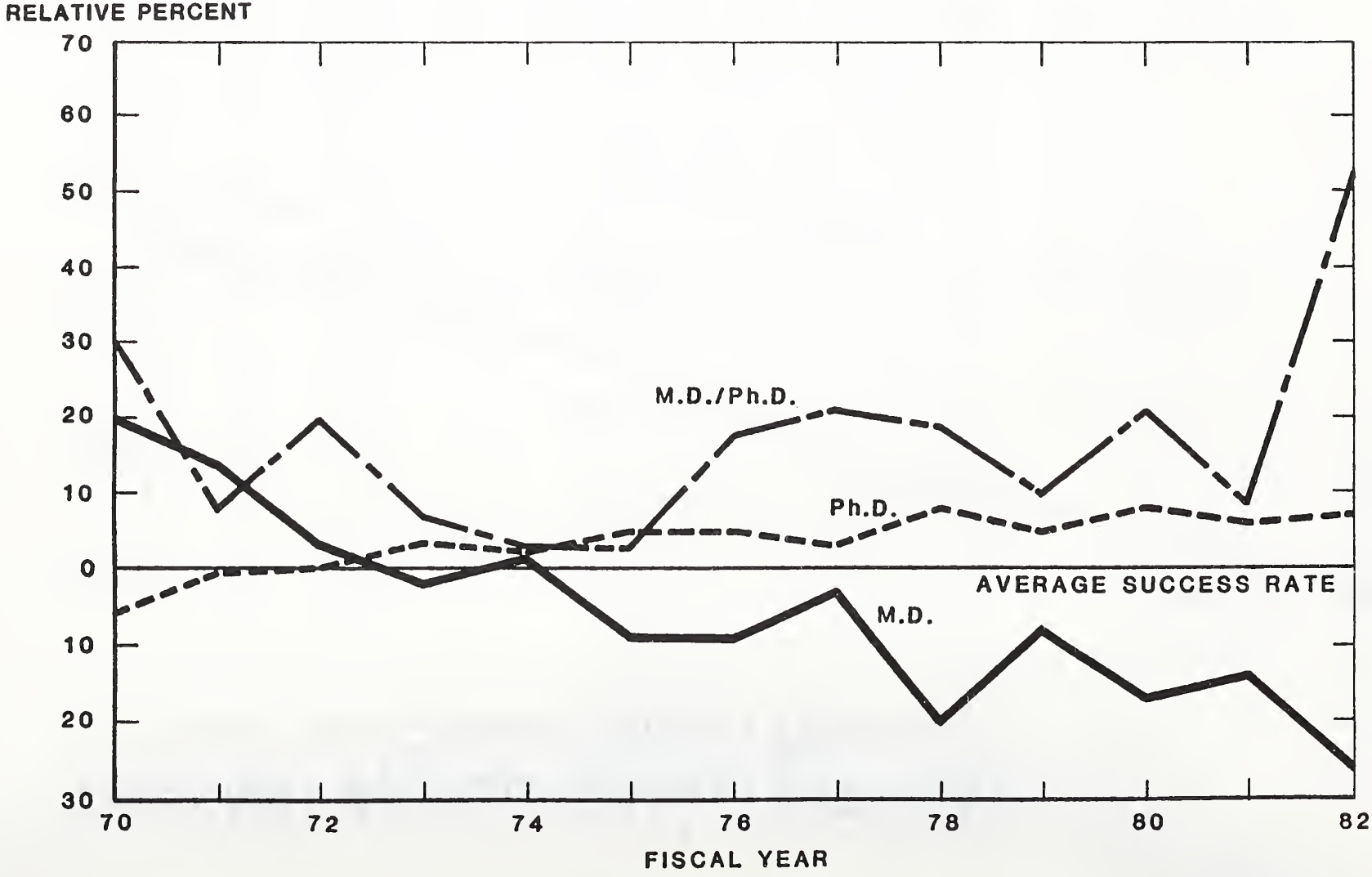
Total NIH Appropriations, 1972-83
In Current and Constant Dollars (Millions)



Prepared by LIRB/DLA/NIH.

Slide 2

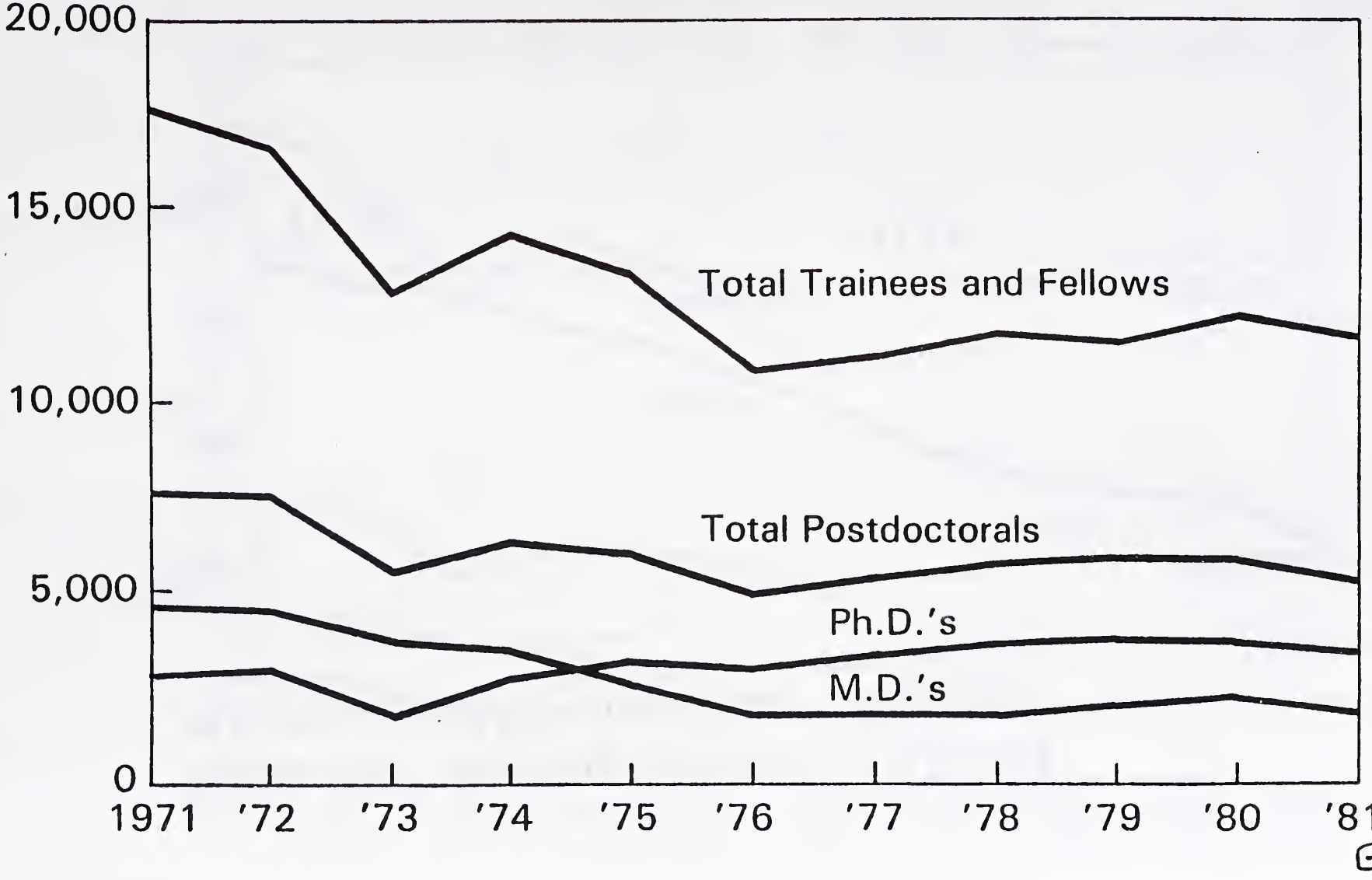
SUCCESS RATES OF NEW M.D., Ph.D., AND M.D./Ph.D. APPLICANTS COMPARED WITH AVERAGE SUCCESS RATES OF ALL NEW R01 APPLICANTS IN THE SAME YEAR



Source: RAEB/DRG/NIH.

Slide 3

TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81



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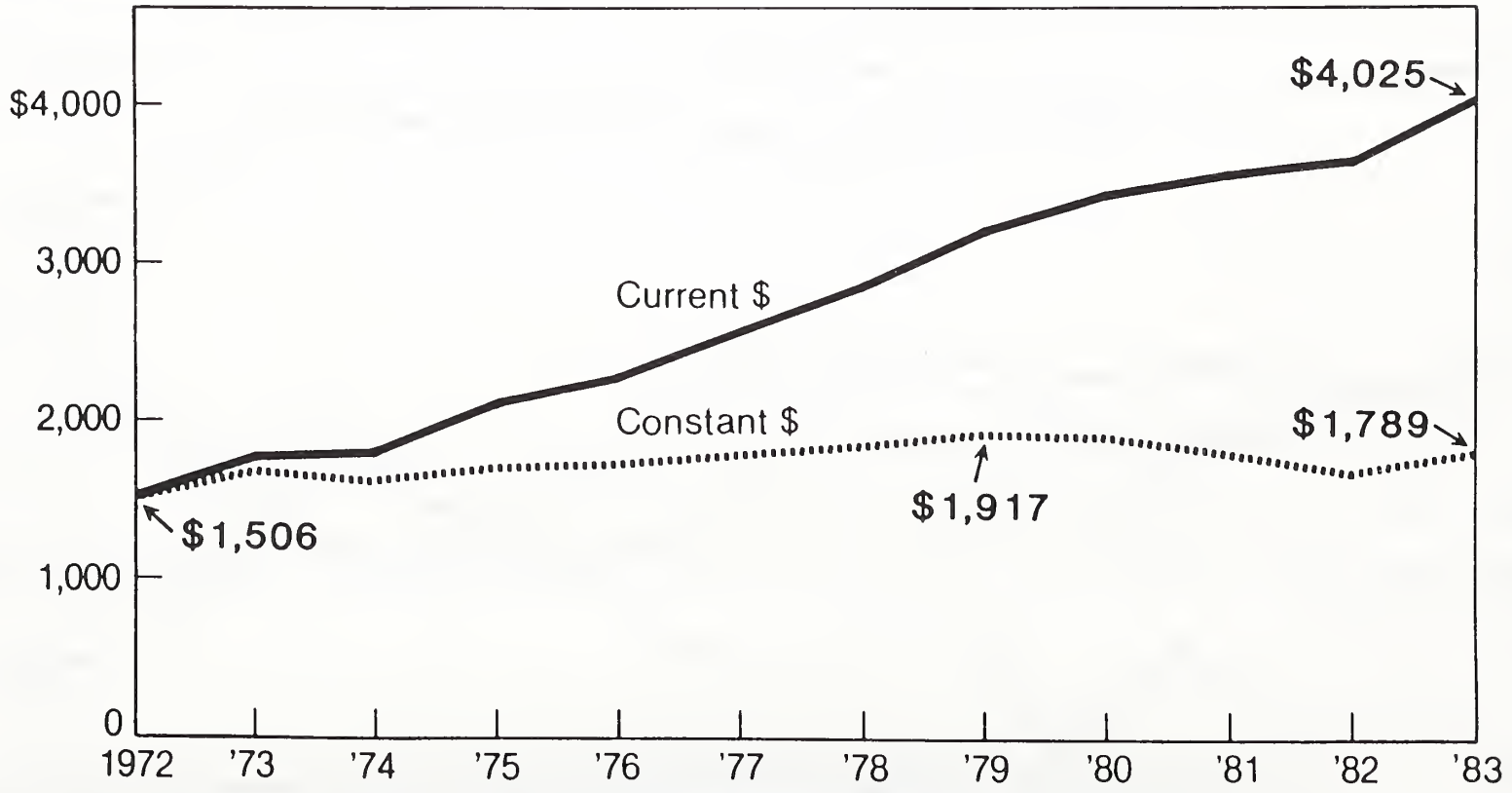
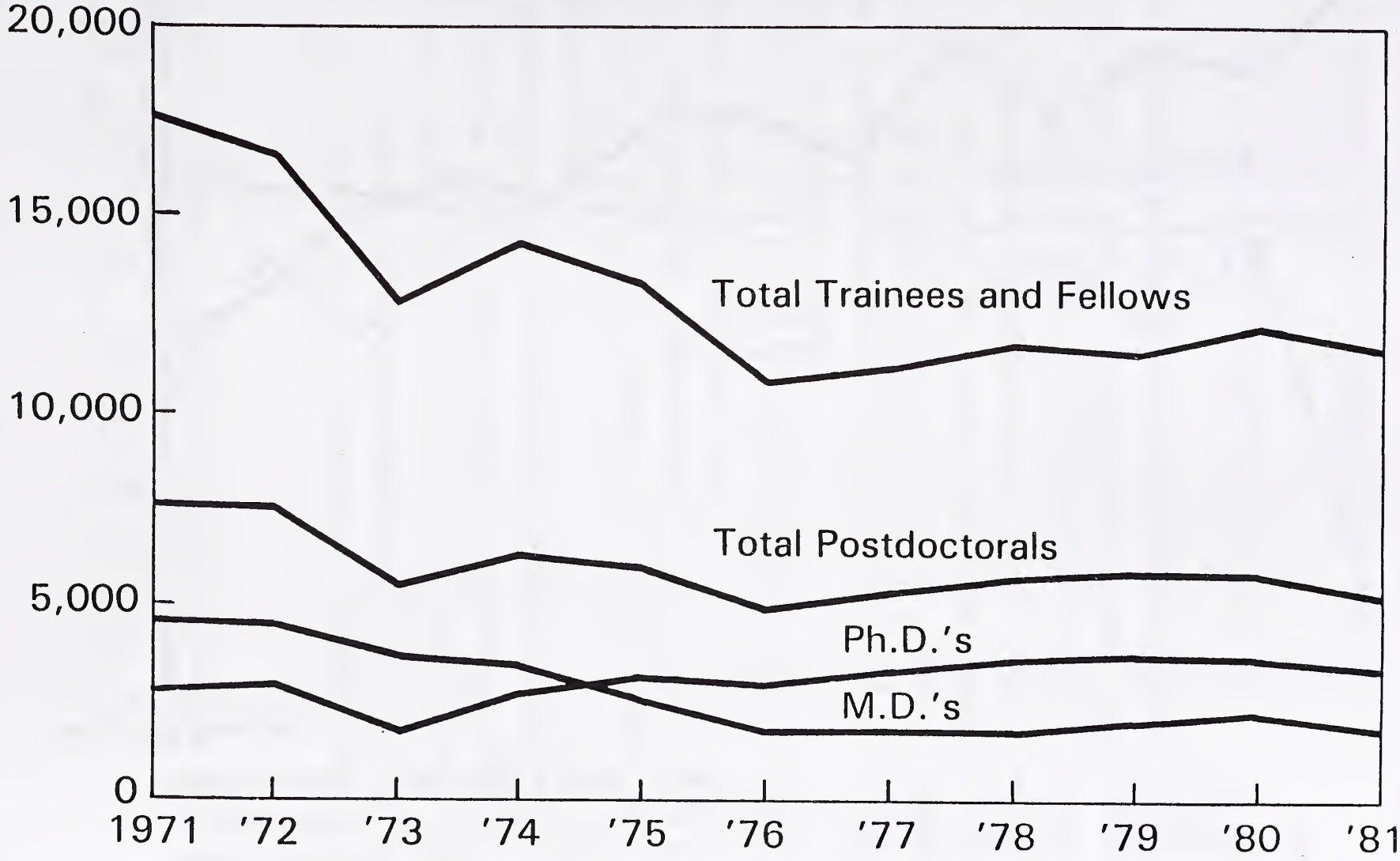
Total NIH Appropriations, 1972-83
In Current and Constant Dollars (Millions)



Prepared by LIRB/DLA/NIH.

Slide 3

TRAINEES AND FELLOWS ON NIH RESEARCH TRAINING AWARDS 1971-81



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Slide 2

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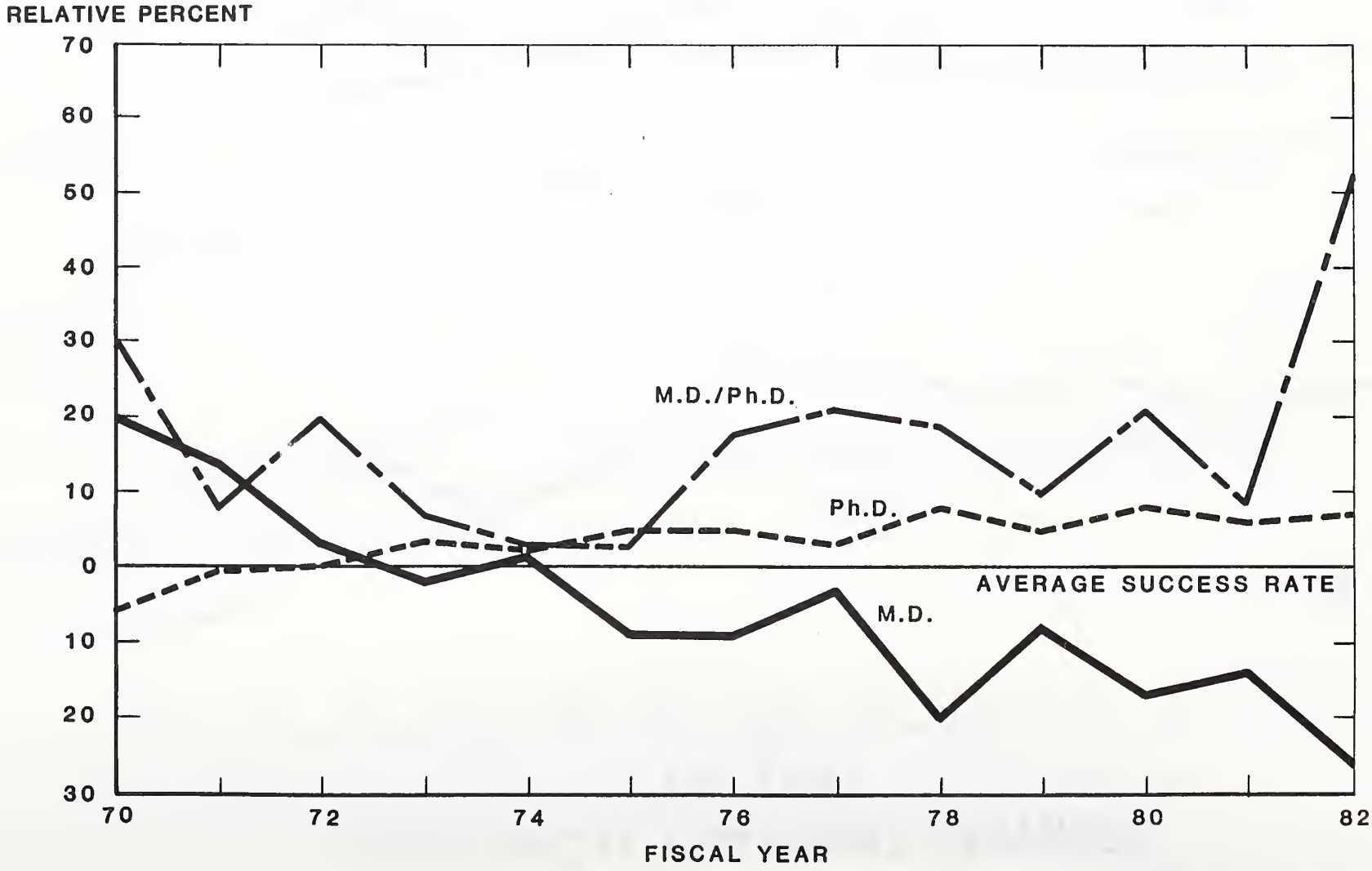

Source: RAEB/DRG/NIH.

REMARKS*

by

James B. Wyngaarden, M.D.**

Tonight gives me two opportunities to act on behalf of others. The first is to carry on for Jim Shannon -- a pleasure since it is what I also do in real life. Jim had planned to be here this evening but the heavy snow in Denver and the bad weather in Chicago forced him to be a "standby" midway in flight from Portland, Oregon, to Washington. He asked that I express his regrets to you. Were he here, I was going to say to him: "Jim, even though a couple of other fellows developed the LINC, you certainly did play an important part in getting it launched."

Actually, I am told that Jim Shannon was in California some 20 years ago. He was shown what (he learned later) was a "form" of computer. His namesake, Claude Shannon, had shown it to him. Jim, on his return to NIH, called a meeting of his scientific directors and no one could think of any use for such an item.

He then made an offer to the universities that NIH would support any predocs with three years of computer training. But there were no takers. And as most of you know, he did establish a task force to bring NIH into the modern era of technology which, after many meetings, brilliant designing and great effort resulted in the product that has brought us together this evening.

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*Presented at the Banquet in Celebration of the 20th Anniversary of the Laboratory Instrument Computer (LINC), Marriott Hotel November 29, 1983, Bethesda, Maryland

**Director, National Institutes of Health, Bethesda, Maryland.

At the entrance of the NIH Clinical Center's Amphitheater, where the Symposium will be held tomorrow, is one of the original LINC computers. I am also told that there is an operational LINC still in existence which has only been "down" four times in 20 years.

Second, it is a special pleasure of my evening to act on behalf of the National Institutes of Health in honoring the creators of the LINC computer -- Mr. Wesley Clark and Dr. Charles Molnar. The LINC and its progeny are dramatic testimony to the power of a good idea. The LINC experience also demonstrates both the importance of public funding in the earliest phases of research and development and the capacity of the private sector to translate, refine, and extend those research results for broad social and economic payoff. There may be no better example of how effectively the public and private sectors can interact than in the triumph we celebrate this evening.

In commemoration of this event, I therefore present to Wesley Clark and Charles Molnar these certificates. They symbolize our admiration for what you have done and the creative energies that enabled you to do it. We hope these certificates will remind you always of the high esteem in which you are held by the scientific community in general and by the National Institutes of Health in particular.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

It is a pleasure indeed to welcome you to this Twentieth Anniversary Retrospective Symposium on the Laboratory Instrument Computer.

Most of the time, those of us who are involved in the excitement of research focus our attention on the future--but for a while today we will be looking backward to the fascinating history of the beginnings of the LINC. It is an interesting and instructive saga, and its significance is only now being realized. As to the future potential of this kind of powerful tool, we can speculate with confidence--which is what "Scotty" Pratt will do with his usual vigor as the last speaker of the day.

Early this year, Nobel Laureate Arthur Kornberg, who is a member of the NIH Director's Advisory Committee, sent me copies of some recent articles he had written on subjects being discussed in the Committee. In a paper on "Biology and Technology," Dr. Kornberg made several observations highly appropriate to our considerations today. Permit me to quote from one of his statements. "We recognize," he said, "that science and technology are interdependent and often inextricably linked. We know that advances in science depend on techniques; the widespread use of techniques in turn depends on innovative and aggressive commercial development. When advanced instrumentation and fine biochemicals become commercially available and affordable, research is extended a thousandfold."

Beyond its effect in extending the capability of the scientist to probe more deeply into the well-hidden secrets of nature, the impact of the LINC on the computer industry is a different but noteworthy success story. Later this morning we will hear highlights from that story.

The planners of today's symposium have put together an unusually strong program and have selected as moderator an exceptional individual, Dr. Eugene A. Stead, Jr. Dr. Stead has had several notable careers. He was Chairman of the Department of Medicine and Dean of the Medical School at Emory University in Atlanta when still in his thirties. He was Chairman of the Department of Medicine at Duke University for 20 years, building one of the outstanding departments in the country. He was my chief for 10 years and one of the main reasons I went to Duke from NIH in 1956.

He was himself a notable cardiovascular scientist and during his years at Duke, catalyzed the development of cardiovascular research and training in several departments of the school. Duke is still one of the premier centers in the world in cardiovascular work.

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*Welcome and Introduction of Moderator, Dr. Eugene A. Stead, Jr., at Symposium on the Laboratory Instrument Computer, National Institutes of Health, ACRF, Bethesda, Maryland, November 30, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

When Gene retired as Chairman of Medicine, early by his own choice, he became a Distinguished Physician at the Durham VA Hospital and also served as editor of Circulation. He recently retired as Distinguished Professor and now serves in yet another career as editor of the North Carolina State Medical Journal.

But the accomplishment which has earned for him the honor of chairing this morning's session is his establishment of the Duke University Computerized C.V. Data Bank in the mid 1960s. Dr. Stead realized the immense potential of the computer for handling clinical and physiological data and applied this new tool to all patients of coronary artery disease studied at Duke Hospital. Gene realized that patients could be grouped according to common descriptors -- 1,2,3 vessel disease, AVO_2 differences, presence or absence of dyskinetic myocardial segments, etc., and that like patients were apt to have like prognoses. This system now has about 7,000 patients entered into it and is proving exceedingly valuable for cardiovascular epidemiology and also for clinical decision making, and for analyses of clinical trials.

Gene has also captured numerous prizes and recognitions throughout his long and productive career. In fact I thought he had already received almost every prize that it was possible for him to win -- but yesterday I heard of one more to be awarded to Dr. Stead this spring -- the Sheen Prize for outstanding contribution to medicine.

Gene is also no stranger to NIH, having served on numerous committees, boards and councils over the years. Gene, it is a pleasure to welcome you to chair the opening session of this symposium.

THE ROLE OF THE U.S. NATIONAL INSTITUTES OF HEALTH IN THE TRAINING OF AMERICAN MEDICAL SCIENTISTS*

by

JAMES B. WYNGAARDEN, M.D.**

I AM VERY HAPPY TO BE HERE TODAY TO TALK TO THIS GROUP ABOUT NIH'S ROLE IN TRAINING ACADEMIC MEDICAL SCIENTISTS. EVEN BEFORE I CAME TO NIH AS DIRECTOR, I WAS INTERESTED IN THE TRAINING OF RESEARCH SCIENTISTS AND SERVED ON THE NATIONAL ACADEMY OF SCIENCE'S COMMITTEE ON PERSONNEL NEEDS AND TRAINING FOR BIOMEDICAL AND BEHAVIORAL RESEARCH. AS NIH DIRECTOR, MY INTEREST IN THIS AREA REMAINS HIGH AND THIS YEAR I HAVE SPOKEN TO VARIOUS GROUPS ABOUT RESEARCH TRAINING NEEDS, ESPECIALLY THE TRAINING OF PHYSICIANS FOR RESEARCH CAREERS.

FORTUNATELY, NIH IS NOT ALONE IN THE IMPORTANCE IT PLACES ON PHYSICIANS IN RESEARCH. WITHIN A PERIOD OF 18 MONTHS THE NUMBER OF PHYSICIANS INVOLVED IN RESEARCH WAS THE THEME OF TALKS BY THE PRESIDENTS OF FOUR MAJOR PROFESSIONAL SOCIETIES: THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION; THE AMERICAN FEDERATION FOR CLINICAL RESEARCH; THE SOCIETY OF UNIVERSITY PHYSICIANS; AND THE ASSOCIATION OF AMERICAN PHYSICIANS. THE CONGRESS, TOO, HAS BEEN INTERESTED: IN ITS REPORT ON THE FISCAL YEAR 1983 BUDGET FOR THE DEPARTMENT OF HEALTH AND HUMAN SERVICES, THE COMMITTEE ON APPROPRIATIONS STATED:[1] "THE COMMITTEE SHARES THE CONCERNS THAT HAVE BEEN EXPRESSED BY OFFICIAL AND PUBLIC WITNESSES ABOUT THE DIFFICULTY OF RECRUITING AND RETAINING PHYSICIANS FOR RESEARCH CAREERS, ESPECIALLY AS ALL CLINICAL RESEARCH, INVOLVING HUMAN PATIENTS, MUST BE DONE BY--OR, AT LEAST, UNDER THE GUIDANCE AND SUPERVISION OF--A QUALIFIED PHYSICIAN. THE COMMITTEE WOULD LIKE NIH TO REVIEW THIS PROBLEM CAREFULLY AND TO SUGGEST WHAT STEPS MIGHT USEFULLY BE TAKEN TO INCREASE THE NUMBER OF YOUNG PHYSICIANS WHO WILL APPLY FOR RESEARCH TRAINING AND TO RETAIN THOSE WHO DO EMBARK ON RESEARCH CAREERS.

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*Address, the American Orthopaedic Fourth International Conference at the Hershey Hotel, Hershey, Pennsylvania, December 1, 1983.

**Director, National Institutes of Health, Bethesda, MD.

ALMOST EVERYONE CAN APPRECIATE THE CONTRIBUTIONS TO HUMAN HEALTH GAINED THROUGH THE "BENCH TO BEDSIDE" CONNECTION. CLEARLY, WE NEED PHYSICIAN SCIENTISTS TO ENSURE THAT THE GREAT FUNDAMENTAL ADVANCES--THE INSPIRING ADVANCES--ARE APPROPRIATELY APPLIED TO PROBLEMS IN HUMAN HEALTH. BUT, IN ORDER FURTHER TO ADVANCE BIOMEDICAL SCIENCE AND CONTINUE TO IMPROVE HEALTH, THE PATH OF INQUIRY MUST ALSO FLOW IN THE OPPOSITE DIRECTION--FROM "BEDSIDE TO BENCH."

I AM THINKING NOW OF THE TYPE OF RESEARCH DONE BY RECENT WINNERS OF THE HAZEN AWARD FOR CLINICAL RESEARCH: JESSE ROTH FOR EXPLAINING THE BASIC DEFECT IN CELL RECEPTORS IN DIABETES OF THE OBESE; HENRY KUNKLE FOR DEMONSTRATING THE ROLE OF CIRCULATING IMMUNE COMPLEXES IN DISEASE; AARON LERNER FOR EXPLAINING THE BIOLOGY OF BENIGN AND MALIGNANT PIGMENT CELLS; JOSEPH GOLDSTEIN AND MICHAEL BROWN FOR ELUCIDATING THE LDL RECEPTOR PATHWAY; AND THIS YEAR, ROBERT LEFKOWITZ FOR SHAPING THE FIELD OF DRUG AND HORMONE RECEPTOR RESEARCH. OR, ONE COULD CITE RECENT LASKER AWARD WINNERS IN CLINICAL RESEARCH, SUCH AS THE NIH RECIPIENTS--ELIZABETH NEUFELD FOR ELUCIDATING THE METABOLIC DEFECTS OF THE MUCOPOLYSACCHARIDOSES, AND ROSCOE BRADY FOR HIS CONTRIBUTIONS TO THE BIOCHEMISTRY AND EXPERIMENTAL THERAPY OF CERTAIN LIPID STORAGE DISEASES. IN THIS TYPE OF RESEARCH, THE CLINICAL QUESTION IS THE CENTRAL FORCE OF THE INVESTIGATION. THIS WORK IS A MOST EXCITING TYPE OF RESEARCH, REQUIRING SOMEONE WHO IS BOTH MEDICALLY KNOWLEDGEABLE AND SCIENTIFICALLY TRAINED.

BUT THE TWO-WAY FLOW FROM BASIC SCIENCE TO CLINICAL APPLICATION AND FROM CLINICAL OBSERVATION TO BASIC SCIENCE DOES NOT SIMPLY OCCUR. IT REQUIRES PREPARATION, SUSTAINED SUPPORT AND, ABOVE ALL, A CONDUCIVE INSTITUTIONAL ATMOSPHERE. FOR ALMOST HALF OF ITS HISTORY, NIH HAS CONSIDERED THE ACADEMIC INSTITUTIONS AS ITS APPROPRIATE PARTNERS IN CARRYING OUT THE NATIONAL MANDATE TO SUPPORT RESEARCH AND IMPROVE HUMAN HEALTH. THE BEDROCK MECHANISM OF SUPPORT IN THIS NIH-MEDICAL SCHOOL PARTNERSHIP HAS BEEN AND WILL CONTINUE TO BE THE RESEARCH PROJECT GRANT TO INDIVIDUAL INVESTIGATORS, REVIEWED FOR MERIT BY SCIENTIFIC PEERS. BUT WE ALSO REALIZE THAT WE HAVE COROLLARY OBJECTIVES--THE STRENGTHENING OF THE INSTITUTIONS IN WHICH THE BIOMEDICAL RESEARCH IS DONE, AND THE DEVELOPMENT OF TRAINING MECHANISMS THAT WILL ENSURE A CONTINUING SUPPLY OF COMPETENT SCIENTISTS DRAWN FROM THE BEST AND THE BRIGHTEST IN THE UNIVERSITIES.

IN ADDITION TO PROVIDING A CONSTANT FLOW OF NEW, YOUNG TALENT, THE ACADEMIC INSTITUTION HISTORICALLY HAS AN ADDITIONAL CHARACTERISTIC THAT MAKES IT A NATURAL ENVIRONMENT FOR RESEARCH--A TRADITION OF ACADEMIC FREEDOM THAT PROTECTS THE ABILITY OF THE RESEARCHER TO FOLLOW LEADS AS HE OR SHE IS DRAWN.

THE ACADEMIC HEALTH CENTER HAS MUCH TO GAIN FROM ITS RESEARCH COMPONENT. THE LINKING OF RESEARCH AND TEACHING IS VALUABLE TO BOTH ENTERPRISES. EDUCATION IS ENHANCED IF IT EXPOSES STUDENTS TO COMMITTED SCHOLARS AND RESEARCHERS. MOREOVER, THE RESEARCH ENTERPRISE ALSO GAINS, FOR STUDENTS WITH FRESH IDEAS OFTEN STIMULATE THEIR MENTORS IN THE EXPLORATION OF NEW AVENUES. THE HEALTH CARE COMPONENT OF THE ACADEMIC CENTER AND THE RESEARCH UNDERTAKING ALSO PROVIDE MUTUAL ENHANCEMENT.

THE AUDITORIUM OF THE NIH CLINICAL CENTER HAS A QUOTATION CARVED IN THE MARBLE WALL AT ITS ENTRANCE, A QUOTATION FROM ITS FIRST DIRECTOR, DR. JACK MASUR, THAT BEAUTIFULLY CAPTURES THIS CONCEPT. IT READS: "HOSPITALS WITH LONG TRADITIONS OF EXCELLENCE HAVE DEMONSTRATED ABUNDANTLY THAT RESEARCH ENHANCES THE VITALITY OF TEACHING; TEACHING LIFTS THE STANDARDS OF SERVICE; AND SERVICE OPENS NEW AVENUES OF INVESTIGATION."

JUST HOW MANY PHYSICIANS WE NEED TO DEVOTE THEMSELVES TO RESEARCH IS, OF COURSE, NOT KNOWN. JUST HOW MANY WE NEED IN EACH DISCIPLINE CANNOT BE ESTIMATED. BUT CLEARLY, THE BURGEONING OF BASIC KNOWLEDGE IN THE PAST DECADE HAS OPENED UP VAST AREAS FOR CLINICAL RESEARCH, AND MANY ARE CONCERNED ABOUT THE DIMINISHING SHARE OF PHYSICIANS WHO ARE INTERESTED IN APPLYING THEMSELVES TO THE CLINICAL RESEARCH NEEDS OF TOMORROW. SOME QUANTITATIVE DATA MAY SERVE TO EMPHASIZE OUR CONCERN AND MAY POINT TO SOME ACTIONS THAT MAY ALLEVIATE THE SITUATION, AT LEAST TO SOME EXTENT.

(SLIDE 1) THE ABSOLUTE NUMBER OF NIH RESEARCH GRANTS (RO1'S) AWARDED TO M.D.'S FELL FROM ABOUT 3,400 IN 1968 TO ABOUT 2,500 IN 1973. THERE HAS BEEN SOME RECOVERY SINCE, BUT THE NUMBER WAS STILL BELOW 3,000 IN 1982. THE NUMBER OF GRANTS TO MD/PH.D.'S (AND THESE ARE, OF COURSE, IN MUCH SMALLER NUMBERS) IS HOLDING RATHER STEADY.

(SLIDE 2) THE PERCENTAGE OF M.D.'S HOLDING NIH RESEARCH GRANTS HAS PROGRESSIVELY FALLEN OVER THE YEARS. M.D./PH.D.'S COMPRISE A RELATIVELY SMALL PROPORTION OF THE GRANT HOLDERS AND THIS GROUP HAS REMAINED RELATIVELY CONSTANT. CURRENTLY PH.D.'S HOLD APPROXIMATELY 68 PERCENT OF THE NIH RESEARCH GRANT (RO1) PORTFOLIO WHILE M.D'S HOLD ONLY ABOUT 22 PERCENT. IF MD/PH.D.'S ARE ADDED, THE PERCENTAGE HELD BY THOSE WITH PROFESSIONAL DEGREES CLIMBS TO ABOUT 31 PERCENT. THUS, THE PROPORTION OF RESEARCH GRANTS AWARDED TO M.D. INVESTIGATORS IS ABOUT ONE-HALF THAT OF A DECADE AGO. NIH CURRENTLY FUNDS MORE THAN 16,000 RO1 TYPE

RESEARCH GRANTS, COMPARED WITH 9000 IN 1972. THE INCREMENT IN THE NUMBER OF SUCH GRANTS HAS GONE ALMOST ENTIRELY TO PH.D. APPLICANTS. MEANWHILE, MANY ADDITIONAL M.D.'S ARE PARTICIPATING IN OTHER RESEARCH MECHANISMS, SUCH AS SPECIALIZED RESEARCH CENTERS AND CLINICAL TRIALS.

IN A SIMPLE EXERCISE TO COMPARE THE NUMBERS OF M.D.'S ACTUALLY SUCCEEDING IN GETTING NIH GRANTS (R01'S) AGAINST THE ENTIRE FIELD OF M.D.'S WHO COULD HAVE CHOSEN BIOMEDICAL RESEARCH FOR A CAREER, WE CONSTRUCTED THE NEXT SLIDE: (SLIDE 3).

THE NUMBER OF M.D.'S SERVING AS PRINCIPAL INVESTIGATORS ON NIH INVESTIGATOR INITIATED GRANTS FROM 1968-1982 IS INDICATED BY THE SOLID LINE. AGAINST THAT IS PLOTTED THE NUMBER OF M.D. GRADUATES FOR EACH YEAR STARTING IN 1957. THE 11-YEAR OFFSET REFLECTS THE FACT THAT ON AVERAGE, THE M.D. IN RESEARCH DOES NOT RECEIVE HIS OR HER FIRST INDEPENDENT RESEARCH GRANT UNTIL 11 YEARS AFTER GRADUATION. AS THE SLIDE SHOWS, THE RATIO BETWEEN M.D. PRINCIPAL INVESTIGATORS AND THE NUMBER OF M.D. GRADUATES HAS NOT WIDENED VERY MUCH OVER THE YEARS SHOWN. THESE ROUGH DATA NEED TO BE VIEWED CAUTIOUSLY, HOWEVER. SINCE MEDICAL SCHOOL ENROLLMENT INCREASED DRAMATICALLY AFTER 1968, WE SUSPECT THAT THIS GAP MAY SOON WIDEN.

THE DECLINE IN THE PERCENTAGE OF M.D. INVESTIGATORS WORKING UNDER R01 GRANTS REFLECTS THE SUBMISSION OF FEWER GRANT APPLICATIONS BY M.D. THAN PH.D. SCIENTISTS. IN 1970, M.D.'S COMPRISED ABOUT 30 PERCENT OF THE APPLICANTS; BY 1980, ONLY 24 PERCENT. ANOTHER IMPORTANT FACTOR IS THE INTENSE COMPETITION.

(SLIDE 4) FOR ALL COMPETING RESEARCH GRANT APPLICATIONS, APPROVAL AND AWARD RATES DID NOT DIFFER GREATLY FOR M.D. AND PH.D. APPLICANTS BETWEEN 1974 AND 1982. THE APPROVAL RATE FOR APPLICATIONS SUBMITTED BY PH.D. INVESTIGATORS HAS RUN ONLY THREE OR FOUR PERCENTAGE POINTS AHEAD OF RATES FOR M.D. INVESTIGATORS. OF THE GRANTS APPROVED BY STUDY SECTIONS, THE AWARD RATES (THAT IS, THE CHANCE OF GETTING FUNDED ONCE APPROVED) FOR M.D. AND PH.D. PRINCIPAL INVESTIGATORS ARE VIRTUALLY THE SAME.

(SLIDE 5) HOWEVER, WHEN ONE LOOKS AT THE SUCCESS RATE OF NEW APPLICANTS ALONE, ONE FINDS THAT THERE HAS BEEN A DIVERGENCE SINCE ABOUT 1974, WITH NEW M.D. APPLICANTS COMPETING LESS WELL THAN NEW PH.D. APPLICANTS, WITH BOTH GROUPS COMPETING LESS SUCCESSFULLY THAN THE MD/PH.D. APPLICANT.

(SLIDE 6) THIS TREND IS EVEN MORE DRAMATIC WHEN EXPRESSED IN COMPARISON WITH THE AVERAGE SUCCESS RATE OF ALL RESEARCH GRANT APPLICATIONS OF THAT YEAR, WHICH HAS BEEN GIVEN A SCORE OF 0. NOTE THAT INCREASINGLY, THE GREATEST SUCCESS IS OBTAINED BY THE MD/PH.D. APPLICANT, FOLLOWED BY THE PH.D. APPLICANT AT SOMEWHAT ABOVE THE AVERAGE RATE, AND BY THE M.D. APPLICANT WHO IS INCREASINGLY BELOW THE AVERAGE RATE.

ONE FACTOR THAT MAY BE PLAYING A ROLE IN THE RECORD FOR M.D. APPLICANTS IS THE FACT THAT APPLICATIONS FOR CLINICAL RESEARCH TEND TO FARE LESS WELL THAN BASIC SCIENCE APPLICATIONS IN THE NIH GRANT REVIEW SYSTEM.

CLINICAL RESEARCH APPLICATIONS--THOSE INVOLVING HUMAN SUBJECTS OR HUMAN TISSUES--ARE MORE OFTEN DISAPPROVED AND MORE OFTEN ASSIGNED POORER PRIORITY SCORES THAN ARE APPLICATIONS IN WHICH NO HUMAN SUBJECTS ARE INVOLVED.

AS THE NEXT SLIDE INDICATES, (SLIDE 7), APPROVAL RATES FOR STUDIES THAT DON'T INVOLVE HUMAN SUBJECTS ARE SUBSTANTIALLY HIGHER THAN THOSE FOR STUDIES WITH HUMAN SUBJECTS, REGARDLESS OF WHETHER THE PRINCIPAL INVESTIGATOR IS AN M.D. OR A PH.D.

IN ORDER TO DISCOVER WHY APPLICATIONS TO NIH FOR GRANTS TO CONDUCT CLINICAL RESEARCH MAY EITHER BE DISAPPROVED OR RECEIVE POOR PRIORITY IN THE REVIEW PROCESS, THE DIVISION OF RESEARCH GRANTS EXAMINED 256 APPLICATIONS RATED BY 13 DIFFERENT STUDY SECTIONS.[2] (SLIDE 8) FOR THIS STUDY, CLINICAL RESEARCH WAS NARROWLY DEFINED AS RESEARCH INVOLVING HUMAN SUBJECTS THAT INCLUDED A DOCTOR-PATIENT RELATIONSHIP. IT IS INTERESTING AND IMPORTANT TO NOTE THAT INVESTIGATOR QUALIFICATIONS AND RESOURCES AT THEIR INSTITUTIONS PLAYED A VERY MINOR ROLE IN POOR RATING. FLAWS IN RESEARCH DESIGN AND CONCEPTION OF THE HYPOTHESIS LED TO POOR SCORES FROM REVIEWERS. THE MOST FREQUENT DEFICIENCIES--FAULTY HYPOTHESES AND INAPPROPRIATE EXPERIMENTAL DESIGN--WERE THE SAME FLAWS THAT WERE CITED IN THE BASIC RESEARCH PROPOSALS THAT ARE DISAPPROVED.

THE FACILE EXPLANATION OF THE GREATER DIFFICULTY INHERENT IN WORKING WITH HUMAN SUBJECTS MAY NOT BE THE ENTIRE ANSWER TO THE LOWER APPROVAL RATES FOR PHYSICIAN-INVESTIGATORS. SCIENCE HAS BECOME COMPLEX, THE METHODS INTRICATE AND THE TRAINING PERIOD SO LONG THAT THE PHYSICIAN, EVEN AFTER TWO OR THREE YEARS OF FELLOWSHIP TRAINING, REMAINS LESS WELL-TRAINED THAN THE PH.D. SCIENTIST WHO HAS BEEN TRAINING FOR A RESEARCH CAREER SINCE THE BACCALAUREATE. IN MY VIEW, THE

TRENDS OF THE PAST DECADE REFLECT THE PROGRESSIVE PROFESSIONALIZATION OF BIOMEDICAL RESEARCH, IN PARTICULAR OF CLINICAL RESEARCH. I HOPE THERE WILL ALWAYS BE ROOM FOR THE CREATIVE AMATEUR IN CLINICAL INVESTIGATION, BUT RECENT HISTORY INDICATES THAT SUCH A PERSON IS LESS AND LESS LIKELY TO SECURE EXTERNAL SUPPORT FOR HIS OR HER WORK. SUCCESS FOR AN M.D. INVESTIGATOR IS INCREASINGLY DEPENDENT UPON SUBSTANTIAL TRAINING IN THE INFORMATION, CONCEPTS, AND METHODOLOGIES OF COMPLEX MODERN SCIENCE. TO BE A FIRST-RATE SCIENTIST AND A WELL-QUALIFIED PHYSICIAN IS A DEMANDING CALLING.

CLINICAL RESEARCH REQUIRES EXPERIENCES NOT REPRESENTED IN MOST MEDICAL SCHOOL AND HOUSE STAFF EXPERIENCES. THE QUALITY OF A RESEARCH GRANT IS A REFLECTION OF THE COMPETENCE AND SOPHISTICATION OF THE INVESTIGATOR APPLICANT. AS DAMON RUNYON SAID, "THE RACE IS NOT ALWAYS TO THE SWIFT OR THE BATTLE TO THE STRONG, BUT THAT'S THE WAY TO BET."

THE INTEGRAL RELATIONSHIP BETWEEN TRAINING AND LATER CONDUCT OF RESEARCH SEEMS ALMOST SELF-EVIDENT, BUT I WOULD LIKE TO CITE SEVERAL PIECES OF DATA THAT SUPPORT THIS CONTENTION. ONE STUDY BY THE AAMC[3] HAS SHOWN THAT FOR BOTH M.D.'S AND PH.D.'S, LENGTH OF POSTDOCTORAL TRAINING HAS THE GREATEST INFLUENCE ON APPROVAL RATE ON FIRST RESEARCH GRANT APPLICATIONS, WITH OTHER SIGNIFICANT FACTORS BEING THE INSTITUTION CONFERRING THE DEGREE AND THE PLACE OF EMPLOYMENT.

IN RECENT YEARS, EVEN WITHOUT THE PRODDING OF CONGRESS, NIH HAS BEEN CONSTANTLY REVIEWING ITS PORTFOLIO OF TRAINING AND DEVELOPMENT MECHANISMS IN ORDER TO MONITOR THE STATUS OF PHYSICIAN TRAINEES AND MAKE ADJUSTMENTS THAT WOULD ENCOURAGE PHYSICIANS TO AVAIL THEMSELVES OF RESEARCH TRAINING OPPORTUNITIES.

MANY CONCERNED ABOUT THIS ISSUE NOTE THE SEEMINGLY DRASTIC DECLINE IN M.D. TRAINEES AND FELLOWS FROM ABOUT 4,600 TO 1,900 BETWEEN 1971 AND 1981. THIS DROP IS SOMEWHAT ARTIFICIAL BECAUSE CESSATION OF FEDERAL SUPPORT FOR CLINICAL TRAINING IN THE EARLY 1970'S CERTAINLY CONTRIBUTED TO THE DROP-OFF.

(SLIDE 9) DATA FROM 1975 TO THE PRESENT CORRESPOND TO THE INCEPTION AND DEVELOPMENT OF THE NATIONAL RESEARCH SERVICE AWARD (NRSA) PROGRAM. WE SEE THE DECLINE IN M.D. PARTICIPATION CONTINUING TO FY 1976 AND THEN APPARENTLY LEVELING OFF. AT THE SAME TIME, PH.D. PARTICIPATION HAS GREATLY INCREASED.

THE MODIFICATION IN AUTHORITY IN 1974, UNDER THE NATIONAL RESEARCH SERVICE AWARDS ACT, LIMITS TRAINING EXCLUSIVELY TO RESEARCH OR ACADEMIC DEVELOPMENT. UNDER THE SAME ACT, A COMMITTEE OF THE NATIONAL ACADEMY OF SCIENCES RECENTLY RECOMMENDED IN ITS 1983 REPORT THAT 2,600 CLINICAL RESEARCH TRAINING SLOTS BE OFFERED BY NIH ANNUALLY--2,230 AS TRAINEESHIPS, AND 370 AS DIRECT FELLOWSHIPS. AN EARLIER FIGURE OF 2,800 CLINICAL TRAINING POSITIONS WAS NOT REACHED UNTIL 1980, BUT AT THAT TIME 900 OF THESE CLINICAL TRAINEESHIPS WERE HELD BY PH.D. TRAINEES, (TWICE THE NUMBER ONLY THREE YEARS AGO) AND ONLY 1,900 BY M.D. TRAINEES. THE ACADEMY COMMITTEE ALSO RECOMMENDED THAT AT LEAST 85 PERCENT OF THE TRAINEESHIPS IN THIS CATEGORY, OR NOW ABOUT 2,210, BE FILLED BY M.D.'S. SO, BY EVERY YARDSTICK, WE ARE FAILING TO ATTRACT THE NUMBER OF QUALIFIED PHYSICIANS INTO RESEARCH TRAINING PERCEIVED TO BE DESIRABLE BY THE ACADEMY COMMITTEE. FORTUNATELY, SOME OF THIS GAP IS BEING FILLED BY PH.D. SCIENTISTS INTERESTED IN CLINICAL RESEARCH. BUT THIS SHORTFALL OF PHYSICIAN INVESTIGATORS ALTERS THE BALANCE BETWEEN M.D. AND PH.D. INVESTIGATORS DEEMED ESSENTIAL FOR COORDINATED PROGRESS IN BASIC SCIENCE AND CLINICAL RESEARCH.

AT THE PRESENT TIME, THE STIPENDS AVAILABLE FOR SUPPORT OF NATIONAL RESEARCH SERVICE AWARD TRAINEES ARE PALTRY, WELL BELOW THOSE AVILABLE IN OTHER FEDERAL RESEARCH TRAINING PROGRAMS. PREDOCTORAL STIPENDS SHOULD BE RAISED TO THE $8,100 THAT IS OFFERED BY THE NATIONAL SCIENCE FOUNDATION. POSTDOCTORAL STIPENDS SHOULD BE INCREASED BY A MINIMUM OF $5,000. AN ESTIMATED SUPPLEMENT OF SOME $44 MILLION WOULD BE REQUIRED TO APPROACH PARITY UNDER THE NRSA PROGRAM, WITH OTHER FEDERAL AGENCY SUPPORT OF PRE- AND POSTDOCTORAL TRAINEES. OUR PROGRAMS FOR CANCER DEVELOPMENT WOULD REQUIRE MORE THAN $10 MILLION TO BRING THEIR SALARY LEVELS IN LINE WITH OTHER INDIVIDUALS OF EQUIVALENT TRAINING AND EXPEIENCE.

FULL-TIME TRAINING SLOTS SHOULD REMAIN AVAILABLE FOR THE NRSA PROGRAM TO KEEP IT AT THE LEVEL RECOMMENDED BY THE NATIONAL ACADEMY OF SCIENCES. INCREASES ARE ALSO NEEDED IN THE CAREER DEVELOPMENT PROGRAM AT A RATE OF 200 ADDED AWARDS A YEAR FOR THREE YEARS. THE LATTER INCREASES, PLUS THE INCREASE IN NUMBERS OF NRSA TRAINEES, WOULD REQUIRE AN ADDITION OF SOME $40 MILLION PER YEAR OVER THE PRESIDENT'S REQUEST. THUS, TOTAL NEEDS TO BRING THE SUPPORT TO COMPETITIVE LEVEL AMOUNT TO ABOUT $84 MILLION.

MANY REASONS HAVE BEEN CITED FOR THE DECLINING INTEREST OF PHYSICIANS IN CLINICAL RESEARCH. MOST MEDICAL SCHOOL CURRICULA PROVIDE LITTLE OR NO LABORATORY EXPERIENCE THAT IS REPRESENTATIVE OF MODERN DAY MEDICAL SCIENCE. THE RISE

RISE OF SPECIALTY FIELDS AND THE LENGTHENING OF POSTDOCTORAL TRAINING PROGRAMS HAVE EXTENDED THE CLINICAL TRAINING NECESSARY FOR BOARD CERTIFICATION. THE REQUIREMENTS OF MANY CERTIFICATION BOARDS ARE RATHER INFLEXIBLE AND CERTAINLY DO NOT ENCOURAGE THE POTENTIALLY CREATIVE PHYSICIAN TO ENTER RESEARCH TRAINING. THESE, OF COURSE, ARE MATTERS ABOUT WHICH NIH CAN DO LITTLE.

OTHER CONSIDERATIONS MAY ACT AS DETERRENTS FOR SOME POTENTIAL TRAINEESHIP APPLICANTS. PERHAPS DOMINATING THE ISSUES IS THAT OF THE FINANCIAL DISINCENTIVES, BOTH BETWEEN THE THIRD-YEAR RESIDENCY SALARY AND THE FIRST-YEAR TRAINEESHIP, WHICH NOW EXHIBITS AN AVERAGE GAP OF $6,000, AND THE SUBSTANTIALLY LARGER DIFFERENCES BETWEEN THE INCOME POSSIBILITIES IN RESEARCH AND IN PROCEDURE-ORIENTED PRACTICES OF MEDICINE. AND ESPECIALLY WHEN THE AVERAGE DEBT LOAD INCURRED BY THE GRADUATING STUDENT IS $20,000 OR MORE, THE CUMULATIVE FINANCIAL DISINCENTIVES ARE A MAJOR FACTOR IN DISSUADING POTENTIAL INVESTIGATORS FROM ENTERING THE FIELD. EVEN WITH ITS STEADY-STATE BUDGET, NIH HOPES TO FIND WAYS TO ALLEVIATE SOME OF THESE PRESSURES IN THE NEXT SEVERAL YEARS.

NIH HAS AN IMPRESSIVE BATTERY OF TRAINING AND DEVELOPMENT OPPORTUNITIES FOR PHYSICIANS: AT THE UNDERGRADUATE MEDICAL STUDENT LEVEL, WE HAVE CONTINUED TO GIVE THE MEDICAL SCIENTIST TRAINING PROGRAM (MSTP) TOP PRIORITY IN OUR TRAINING PORTFOLIO.

IN THE MSTP THIS YEAR, WE WILL SUPPORT ABOUT 650 STUDENTS MOVING TOWARD A COMBINED M.D./PH.D. DEGREE. WE REGARD THIS PROGRAM AS ONE OF OUR MOST SUCCESSFUL IN TERMS OF BUILDING UP CLINICAL RESEARCH. THIS SIX-YEAR PROGRAM, SPONSORED BY THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES, MAKES AWARDS TO 24 SCHOOLS FOR STUDENTS WHO SIMULTANEOUSLY EARN THE M.D. AND PH.D. DEGREES. FOLLOW UP EVALUATION OF THE PROGRAM HAS SHOWN THAT 70 PERCENT OF THE GRADUATES HOLD POSITIONS IN ACADEMIC MEDICINE DOING RESEARCH AND ENGAGING IN THE TRAINING OF OTHER PHYSICIANS. THE PROGRAM WILL BE STRENGTHENED TO SUPPORT APPROXIMATELY 700 STUDENTS PER YEAR, RESULTING IN PRODUCTION OF MORE THAN 100 GRADUATES PER YEAR OF THE TYPE OF SCIENTIST CURRENTLY COMPETING MOST SUCCESSFULLY FOR R01 RESEARCH SUPPORT.

THE NIH ALSO HAS A NUMBER OF PROGRAMS THAT PROVIDE EARLY EXPOSURE TO RESEARCH CAREERS. THIS PAST YEAR MORE THAN 1,100 MEDICAL STUDENTS AVAILED THEMSELVES OF OFF-QUARTER TRAINING OPPORTUNITIES SUPPORTED BY NIH IN APPROXIMATELY 70 SCHOOLS OF MEDICINE, DENTISTRY, AND VETERINARY MEDICINE. WITH THE NEW

EXEMPTION OF THE FIRST YEAR OF NRSA SUPPORT FROM PAYBACK OBLIGATION, THE NIH LAST YEAR REINSTITUTED THE POST-SOPHOMORE FELLOWSHIP OR ITS EQUIVALENT, TO PROVIDE A FULL YEAR OF RESEARCH TRAINING WITHIN THE MEDICAL SCHOOL EXPERIENCE UNDER AN NIH FELLOWSHIP OR TRAINEESHIP. THE NIH ALSO OFFERS SUMMER RESEARCH FELLOWSHIPS AT BETHESDA, AND DURING THIS PAST YEAR 52 MEDICAL STUDENTS CONDUCTED LABORATORY RESEARCH AND ATTENDED LECTURES AND SEMINARS AT NIH.

I FIRMLY BELIEVE THAT EARLY EXPOSURE TO RESEARCH CAN BE IMPORTANT IN RECRUITING YOUNG PEOPLE INTO RESEARCH CAREERS. IN A SURVEY OF SENIOR MEDICAL STUDENTS BY THE AAMC[5], STUDENTS WHO EXPRESSED AN INTENTION OF CHOOSING A RESEARCH CAREER SELECTED AS ONE OF THE THREE MOST IMPORTANT MOTIVATING FACTORS, "RESEARCH EXPERIENCE WHILE A PREMEDICAL OR MEDICAL STUDENT." (THE OTHER TWO WERE "OPPORTUNITY TO WORK IN AN ACADEMIC COMMUNITY" AND "CHALLENGE OF SEARCH FOR NEW KNOWLEDGE.") PERHAPS WHAT IS NEEDED IS EXPOSURE TO THE RESEARCH ATMOSPHERE, A GOOD ROLE MODEL, AND A TASTE OF THE EXCITEMENT OF DISCOVERY, TO INSPIRE THE STUDENT OR HOUSE OFFICER TO DOVOTE HIM- OR HERSELF TO RESEARCH.

THE PHYSICIAN WHO HAS COMPLETED FOUR YEARS OF MEDICAL SCHOOL AND ONE-TO-THREE YEARS OF CLINICAL TRAINING IS, BY AND LARGE, ONLY MODESTLY PREPARED WITH RESEARCH SKILLS. EVEN WHERE SUCCESSFUL PARTICIPATION IN ONE OR MORE RESEARCH PROJECTS HAS TAKEN PLACE, THE EXPERIENCE DOES NOT SUBSTITUTE FOR A PLANNED PROGRAM TO DEVELOP RESEARCH EXPERTISE. A SERIES OF NIH AWARDS, CALLED CAREER DEVELOPMENT AWARDS, PROVIDE RESEARCH DEVELOPMENT OPPORTUNITIES TO QUALIFIED INDIVIDUALS WITH DEMONSTRATED RESEARCH POTENTIAL. TWO MECHANISMS HAVE BEEN PARTICULARLY SUCCESSFUL IN THE ATTRACTION OF PHYSICIANS--THE CLINICAL INVESTIGATOR AWARD AND THE SPECIAL EMPHASIS RESEARCH CAREER AWARD. BOTH PROVIDE FOR THREE-TO-FIVE YEARS OF SUPERVISED RESEARCH DEVELOPMENT IN AREAS OF IMMEDIATE INTEREST TO THE FUNDING INSTITUTE. THEY PROVIDE UP TO $30,000 PER YEAR IN SALARY PLUS COMMENSURATE FRINGE BENEFITS AND SOME MODEST AMOUNT OF RESEARCH SUPPORT. THESE PROGRAMS HAVE BEEN SUCCESSFUL AND THUS HAVE DEMONSTRATED A POTENTIAL FOR EXPANSION.

THE NEWEST ADDITION TO THE CAREER DEVELOPMENT AWARD SERIES WAS ANNOUNCED THIS SUMMER. THIS "PHYSICIAN/SCIENTIST" AWARD IS DESIGNED TO PROVIDE FIVE YEARS OF PHASED SUPERVISED RESEARCH TRAINING. THE FIRST TWO-TO-THREE YEARS WILL BE UNDER THE GUIDANCE OF A SPONSOR WHO IS A BASIC SCIENTIST. THE AWARD WILL CARRY A SALARY COMPARABLE TO THAT EARNED BY A MEMBER OF THE INSTITUTION'S HOUSE STAFF WITH EQUIVALENT EXPERIENCE, UP TO TEN PERCENT OF THE BASIC SCIENCE SPONSOR'S

SALARY AND $10,000 FOR RESEARCH COSTS. THE SECOND PHASE, UNDERTAKEN AT A MORE INDEPENDENT LEVEL, WILL PROVIDE UP TO $20,000 TO COVER RESEARCH COSTS. THIS PROGRAM IS DESIGNED SO THAT IT CAN BE INTERRUPTED--WITH THE RESEARCH SLOT RESERVED--SO THAT THE PHYSICIAN/SCIENTIST CAN RETURN TO THE CLINIC AND MAINTAIN CLINICAL SKILLS, MAKING IT, PERHAPS, ESPECIALLY ATTRACTIVE TO INTERESTED SURGEONS.

FOR THOSE OF YOU REPRESENTING ORTHOPEDIC PROGRAMS ABROAD, I WOULD LIKE TO MENTION NIH OPPORTUNITIES FOR FOREIGN SCIENTISTS. WHILE THEY ARE NOT TRAINING PROGRAMS AS SUCH, THESE PROGRAMS CERTAINLY PROVIDE A RICH ENVIRONMENT FOR TRAINING IN SPECIAL AREAS. THROUGH THE VISITING AND GUEST RESEARCHER PROGRAMS, NIH INVITES APPROXIMATELY 1,400 SCIENTISTS FROM ABOUT 60 COUNTRIES TO WORK IN ITS LABORATORIES IN COLLABORATION WITH NIH INVESTIGATORS. UNDER THE NIH INTERNATIONAL RESEARCH FELLOWSHIP PROGRAM, SCIENTISTS IN THE FORMATIVE STAGES OF THEIR CAREERS CONDUCT COLLABORATIVE PROJECTS IN U.S. BIOMEDICAL RESEARCH INSTITUTIONS. IN 1984, APPROXIMATELY 80 SCIENTISTS FROM ABOUT 50 PARTICIPATING COUNTRIES ARE EXPECTED TO WORK WITH U.S. SCIENTISTS AT VARIOUS INSTITUTIONS THROUGHOUT THE UNITED STATES.

WHILE NIH PROGRAMS AND POLICIES WILL UNDOUBTEDLY HAVE A MAJOR IMPACT UPON THE FUTURE OF CLINICAL INVESTIGATION IN THIS COUNTRY, MAINTENANCE AND GROWTH OF THIS FIELD IS THE OBLIGATION OF ACADEMIC MEDICINE, THE MEDICAL PROFESSION AND ITS PROFESSIONAL SOCIETIES, INDUSTRY, AND OTHER PARTS OF THE PRIVATE SECTOR. SOME MEDICAL SCHOOLS--FOR EXAMPLE, CASE WESTERN RESERVE, DUKE UNIVERSITY, UNIVERSITY OF PENNSYLVANIA, AND OTHERS--HAVE DEVELOPED CURRICULA WITH THE ASPIRING CLINICAL INVESTIGATOR IN MIND. PRIVATE SECTOR ENTITIES SUCH AS THE AMERICAN CANCER SOCIETY, THE AMERICAN HEART ASSOCIATION, AND THE HARTFORD FOUNDATION HAVE ESTABLISHED SPECIAL AWARDS FOR PHYSICIAN SCIENTISTS. ALL OF THESE EFFORTS CONTINUE TO MITIGATE THE CIRCUMSTANCES WHICH SEEM TO BE HINDERING THE GROWTH OF CLINICAL INVESTIGATION.

IN ADDITION, THE CURRENT GENERATION OF CLINICAL INVESTIGATORS HAS A SPECIAL RESPONSIBILITY TO PORTRAY THE SATISFACTIONS THAT CAN COME FROM CLINICAL RESEARCH AS A CAREER. WE NEED TO LET STUDENTS KNOW THAT IN CLINICAL RESEARCH THERE IS OPPORTUNITY TO BE A CAPABLE AND CARING CLINICIAN, AND ALSO TO SHARE IN THE EXCITEMENT THAT COMES FROM DISCOVERY.

BEYOND THE PERSONAL GRATIFICATION THAT COMES FROM CREATIVE WORK, CLINICAL RESEARCH OFFERS THE CHANCE TO CONTRIBUTE BOTH TO THE HEALTH OF INDIVIDUAL

PATIENTS, AND OF GROUPS OF PEOPLE. WE MUST KEEP STRESSING THAT FOR THOSE EXCEPTIONAL STUDENTS WHO WILL TAKE ON THE CHALLENGE OF RESEARCH, THE REWARDS ARE GREAT.

I BELIEVE THAT OUR OWN WORDS AND ACTIONS AS CLINICAL INVESTIGATORS ARE CRITICAL TO THE FUTURE OF OUR PROFESSION. IN HIS BOOK, "EXCELLENCE: CAN WE BE EQUAL AND EXCELLENT TOO?", JOHN GARDNER REMARKED THAT THE INFLUX OF EXCELLENT NEW PEOPLE INTO A GIVEN FIELD IN LARGE PART DEPENDS UPON THE MORALE OF THAT FIELD. AND A MAJOR COMPONENT OF OUR COLLECTIVE MORALE IS THE OPTIMISM AND ENCOURAGEMENT WE PORTRAY TO NEWCOMERS AND THOSE ON THE BRINK OF DECISION.

I HOPE I HAVE MADE A CONTRIBUTION TO OPTIMISM THIS AFTERNOON IN CITING THE CONTINUING COMMITMENT OF NIH TO THE TRAINING, DEVELOPMENT AND RESEARCH SUPPORT OF THE CLINICAL INVESTIGATOR.

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[1]Report No. 97-894, 97th Congress, 2nd Session, House of Representatives, "Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 1983," September 29, 1982.

[2]Janet Cuca, "NIH Grant Applications for Clinical Research: Reasons for Poor Ratings or Disapproval," Division of Research Grants, NIH, September 1982.

[3]Charles R. Sherman, Ph.D., and Thomas E. Morgan, M.D., "Education Patterns and Research Grants Success of Medical School Faculty." An evaluation study prepared for the NIH by the Association of American Medical Colleges, January 1979.

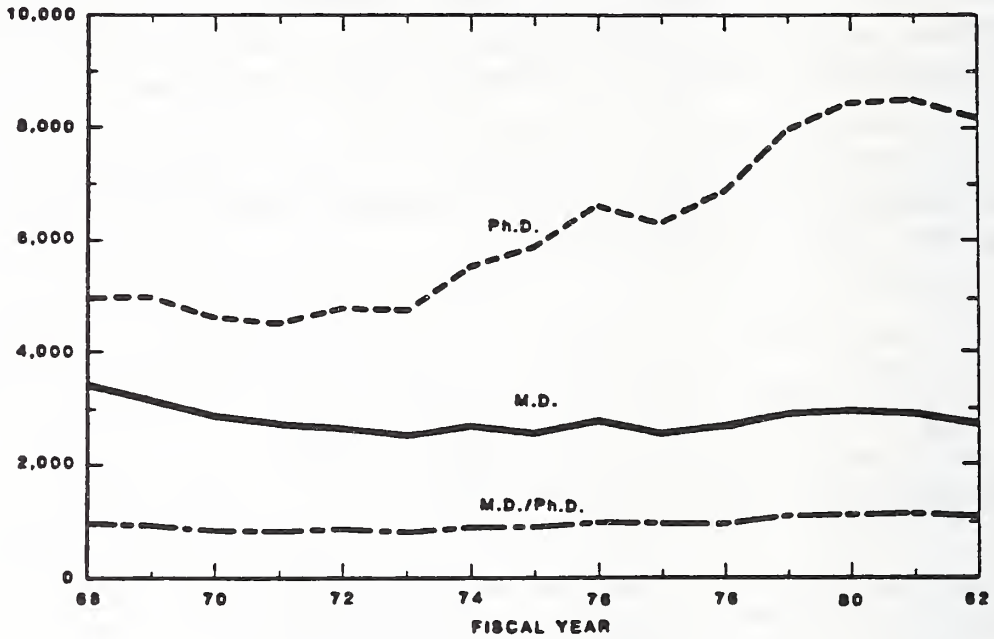
[4]Office of Program Analysis Note No. 6, "Competing Grant Applications from NRSA Trainees," Office of Program Planning and Evaluation, Office of the Director, NIH, October 1982.

[5]NIH Program Evaluation Report: On the Status of Medical School Faculty and Clinical Research Manpower 1968-1990, NIH Publication No. 82-2458, "A Report to the Clinical Sciences Panel of the Committee on a Study of National Needs for Biomedical and Behavioral Research Personnel," National Academy of Sciences, National Research Council, April 30, 1981.

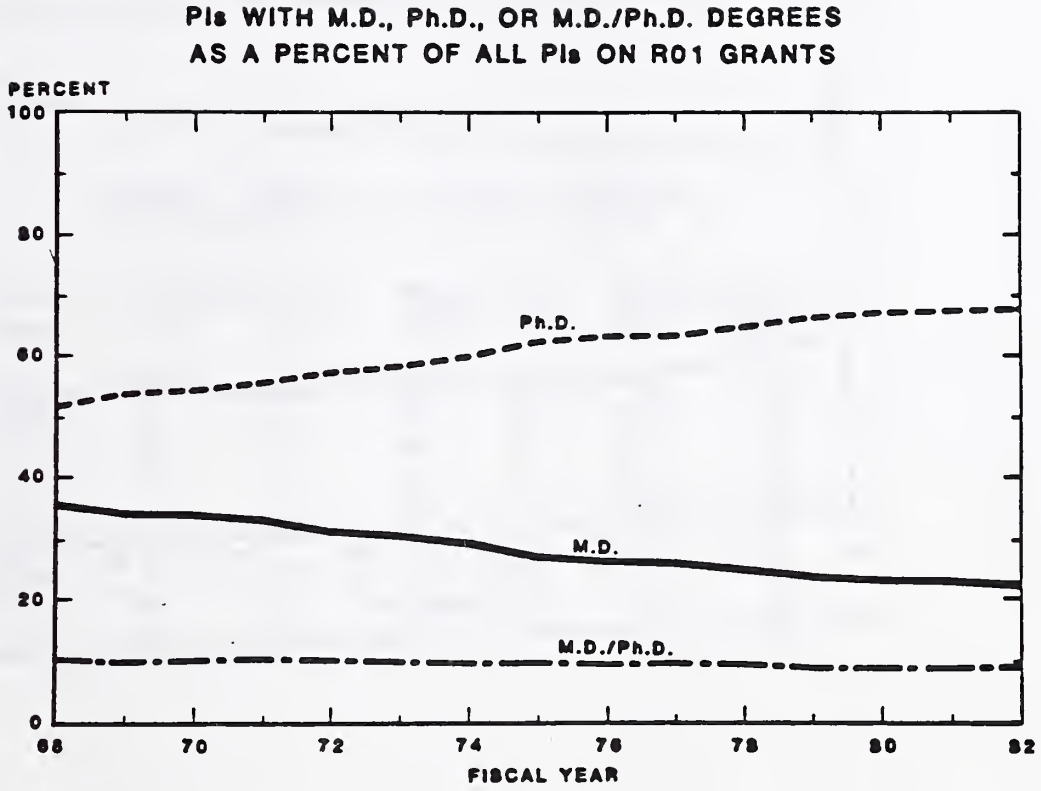
[6]John W. Gardner, "Excellence: Can We Be Equal and Excellent Too?" Harper & Row, Publishers,

SLIDE 1

NUMBER OF PIs WITH M.D., Ph.D., OR M.D./Ph.D. DEGREES ON ALL R01 GRANTS

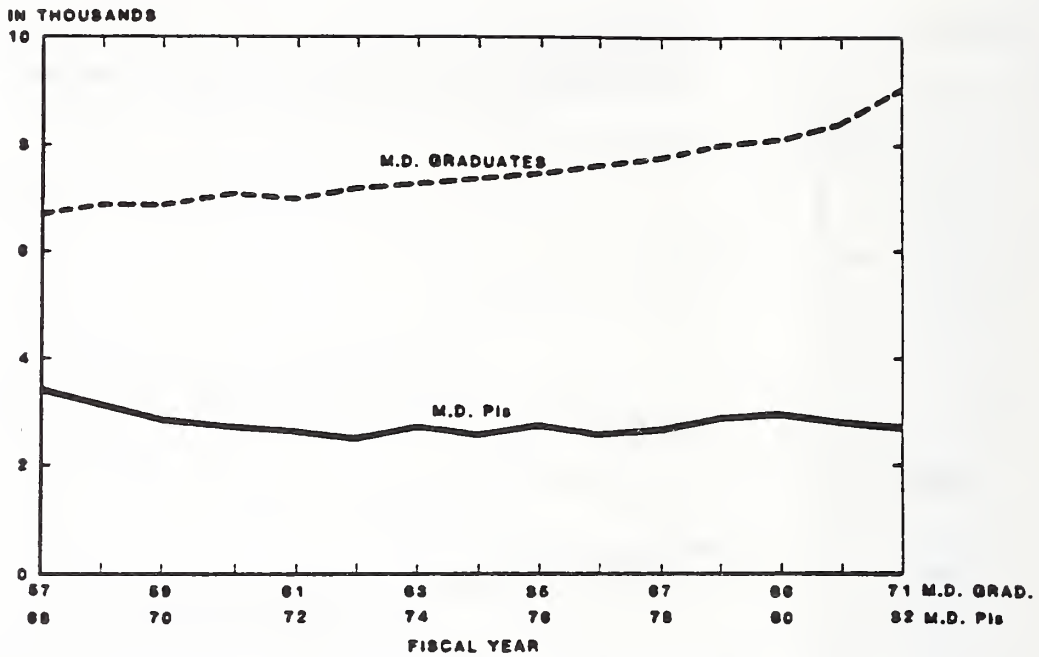


SLIDE 2


PIs WITH M.D., Ph.D., OR M.D./Ph.D. DEGREES
AS A PERCENT OF ALL PIs ON R01 GRANTS
PERCENT
100
80
60
40
20
0
Ph.D.
M.D.
M.D./Ph.D.
68
70
72
74
76
78
80
82
FISCAL YEAR

SLIDE 3

NUMBER OF M.D. PIs ON ALL R01 GRANTS COMPARED WITH NUMBER OF M.D.'s WHO GRADUATED 11 YEARS BEFORE*



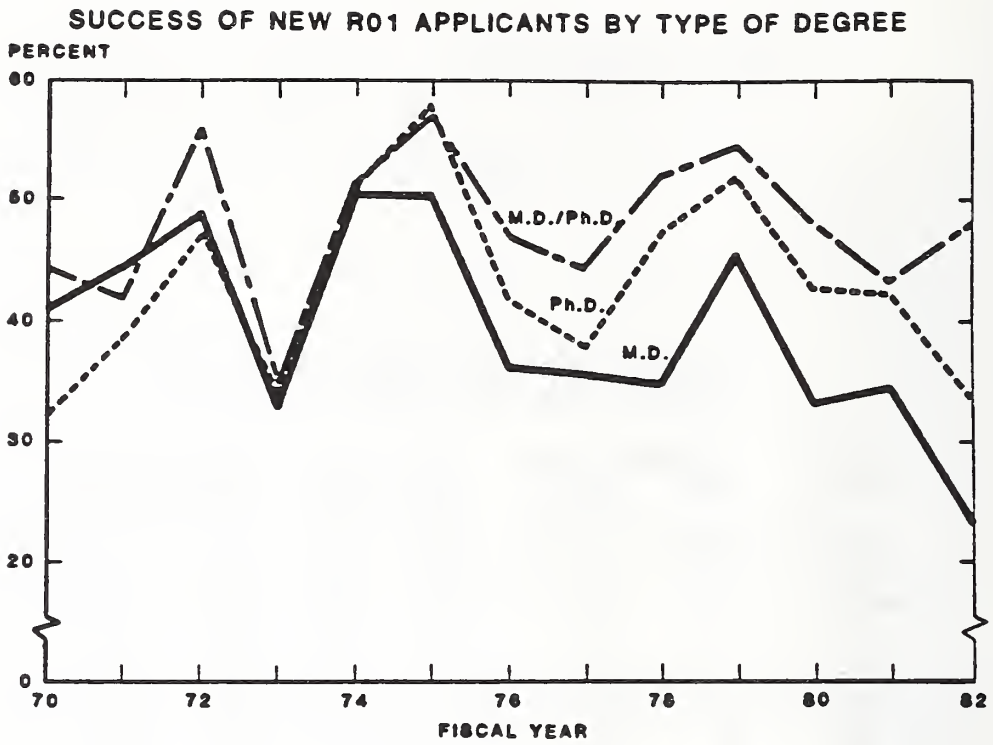
*AVERAGE INTERVAL OF 11 YEARS BETWEEN MEDICAL SCHOOL GRADUATION AND START OF FIRST GRANT.

SLIDE 4

APPROVAL, AWARD, AND SUCCESS RATES FOR COMPETING R01 APPLICATIONS, 1974-82

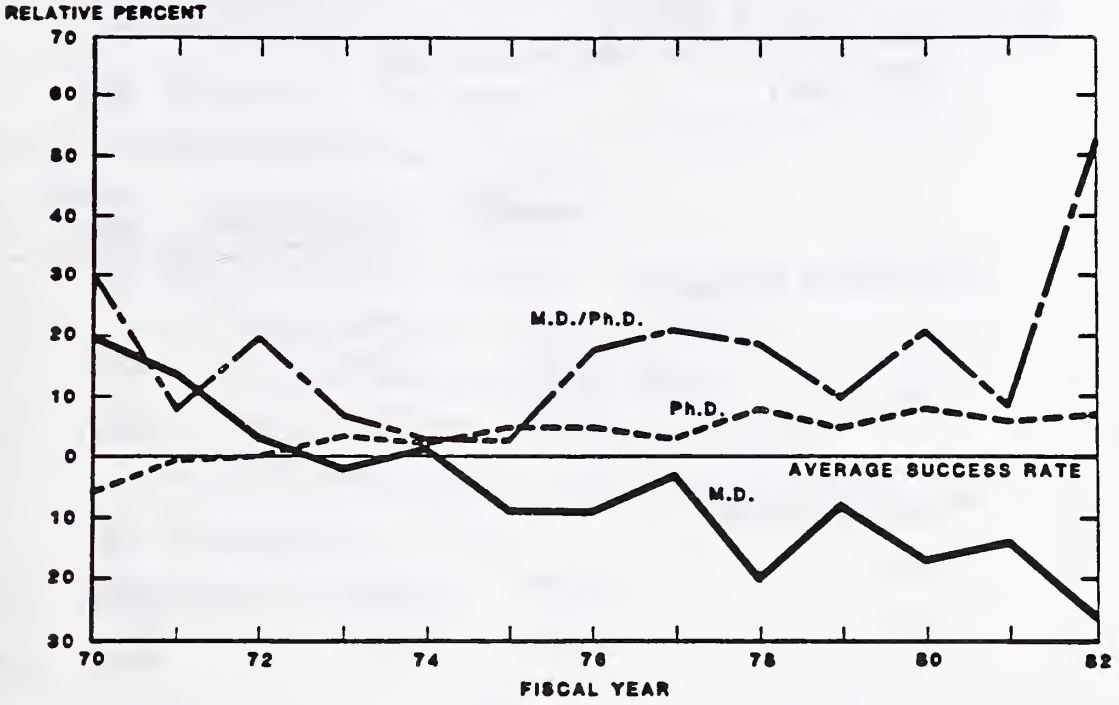
Fiscal year	Approval rate		Award rate		Success rate	
	M.D.	Ph.D.	M.D.	Ph.D.	M.D.	Ph.D.
1974	72%	76%	60%	56%	43%	43%
1975	72	76	60	60	43	46
1976	68	73	50	46	34	34
1977	71	75	41	37	29	28
1978	74	79	45	45	33	36
1979	76	78	50	52	38	40
1980	76	80	42	42	32	33
1981	80	83	40	38	32	32
1982	83	85	34	34	29	29

SLIDE 5


SUCCESS OF NEW R01 APPLICANTS BY TYPE OF DEGREE
PERCENT
60
50
40
30
20
0
70
72
74
76
78
80
82
FISCAL YEAR
M.D./Ph.D.
Ph.D.
M.D.

SLIDE 6

SUCCESS RATES OF NEW M.D., Ph.D., AND M.D./Ph.D. APPLICANTS COMPARED WITH AVERAGE SUCCESS RATES OF ALL NEW R01 APPLICANTS IN THE SAME YEAR



SLIDE 7

Competing R01 Applications 1976-1981

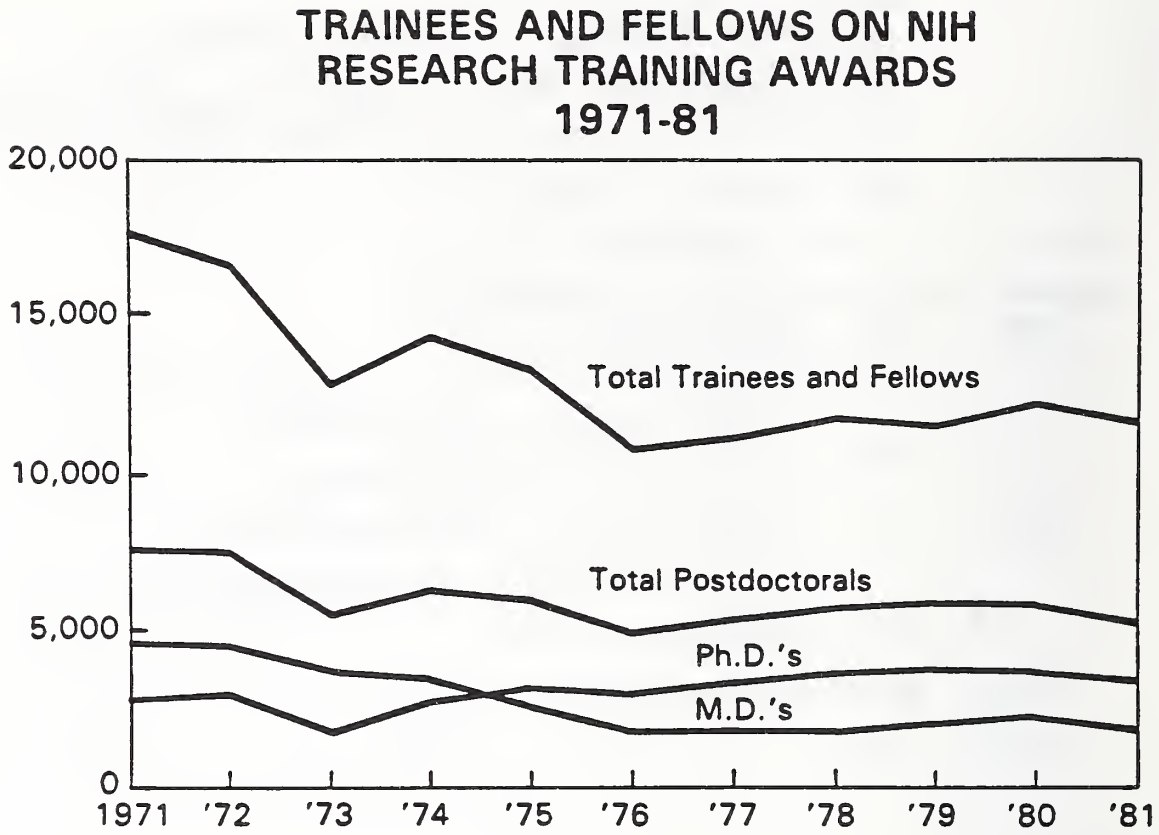
	Number Reviewed	Recommended	Award Rate	Success Rate
No Human Subjects:				
— M.D.	10,552	73%	42%	31%
— Ph.D.	40,815	74%	40%	30%
Human Subjects:				
— M.D.	12,166	64%	39%	25%
— Ph.D.	12,078	61%	38%	23%

SLIDE 8

Shortcomings in Poorly-Rated or Disapproved NIH Grant Applications

- Research Problem:
  - Hypothesis (47%)
  - Significance (30%)
- Experimental Design:
  - Study Group or Controls (40%)
  - Technical Methodology (66%)
  - Data Collection Procedures (41%)
  - Data Management and Analysis (31%)
- Investigator (17%)
- Resources (4%)

SLIDE 9


TRAINEES AND FELLOWS ON NIH
RESEARCH TRAINING AWARDS
1971-81
20,000
15,000
10,000
5,000
0
1971
'72
'73
'74
'75
'76
'77
'78
'79
'80
'81
Total Trainees and Fellows
Total Postdoctorals
Ph.D.'s
M.D.'s

THE ECONOMIC CASE FOR BIOMEDICAL RESEARCH
OR
HOW TO SPEND YOURSELF INTO PROSPERITY*

BY

JAMES B. WYNGAARDEN, M.D.**

WHEN RESEARCH INVESTIGATORS AND ADMINISTRATORS THINK ABOUT THE ECONOMICS OF BIOMEDICAL RESEARCH, THEY USUALLY ARE CONSTRAINED BY CIRCUMSTANCES TO FOCUS ON THE INPUT SIDE OF THE ENTERPRISE--HOW TO OFFER SALARIES THAT WILL ATTRACT AND HOLD BRIGHT YOUNG INVESTIGATORS--HOW TO AFFORD THE ESSENTIAL AND USUALLY EXPENSIVE NEW INSTRUMENTS--WHERE TO FIND THE MONEY TO KEEP A PRODUCTIVE TEAM TOGETHER, AND SO ON AND ON.

IN THE COURSE OF SEEKING FUNDS TO FUEL THE MASSIVE MECHANISM THAT BIOMEDICAL RESEARCH HAS BECOME, WE ARE CONSTANTLY BEING CALLED UPON TO JUSTIFY THE PURPOSES OF THE SUBSTANTIAL INVESTMENT REQUIRED. I DO NOT QUARREL WITH THE NEED TO MAKE THE CASE FOR RESEARCH. IT IS A RESPONSIBILITY WE MUST ACCEPT.

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*Remarks at Massachusetts General Hospital Scientific Advisory Committee Trustees' Dinner-Reception, December 9, 1983.

**Director, National Institutes of Health, Bethesda, Maryland.

THE BURDEN OF OUR APPEAL AND JUSTIFICATION FOR SUPPORT OF BIOMEDICAL RESEARCH HAS EMPHASIZED QUITE PROPERLY THE INTANGIBLE AND INCALCULABLE HUMAN BENEFITS--THE IMPROVEMENTS IN THE QUALITY OF LIFE--THAT HAVE COME FROM RESEARCH. I DO NOT SUGGEST THERE IS ANY BETTER REASON FOR THE CURRENT NATIONAL INVESTMENT OF ABOUT TEN BILLION EACH YEAR IN BIOMEDICAL RESEARCH AND DEVELOPMENT.

BUT THERE IS ANOTHER EFFECT OF BIOMEDICAL RESEARCH--A BENEFIT THAT IS PERHAPS MORE EVIDENT TO ECONOMISTS THAN TO THOSE OF US WHOSE CAREERS HAVE BEEN DEVOTED TO THE BIO-SCIENCES. THE FACT IS THAT WE ARE NOT ACCUSTOMED TO VIEWING BIOMEDICAL RESEARCH AS A FINANCIER MIGHT SCRUTINIZE THE COST BENEFIT TRACK RECORD OF AN INDUSTRY. SUCH AN ANALYSIS IS NOT A SIMPLE TASK.

A FIVE-YEAR STUDY ATTEMPTING TO QUANTIFY THE WORTH OF BIOMEDICAL RESEARCH WAS CONDUCTED IN THE LATE SEVENTIES AND ITS RESULTS WERE PUBLISHED IN 1979 IN A BOOK BY SELMA J. MUSHKIN, TITLED "BIOMEDICAL RESEARCH: COSTS AND BENEFITS." THE STUDY ADDRESSED THE QUESTION, "IS THE PUBLIC GETTING AN APPROPRIATE RETURN FOR THE MULTIBILLION DOLLAR YEARLY EXPENDITURE ON HEALTH RESEARCH?"

THE ANSWER IS AN EMPHATIC "YES." FOR EXAMPLE, WHEN THE MEASURES USED ARE ACTUARIAL ESTIMATES OF THE DOLLAR VALUE OF LIVES SAVED AND WORK YEARS OF SICKNESS AVERTED,

THE RATIO OF TOTAL CUMULATIVE BENEFITS TO TOTAL CUMULATIVE RESEARCH AND DEVELOPMENT COSTS WAS SOMEWHERE BETWEEN 10 TO 1 AND 16 TO 1 FOR THE 75-YEAR PERIOD BEGINNING IN 1900. FOR THE 45-YEAR PERIOD BEGINNING IN 1930, THE RATIO WAS BETWEEN 4 TO 1 AND 6 TO 1. THE MORE RECENT LOWER BUT STILL SPECTACULAR RETURN REFLECTS THE HIGH LEVELS OF BASIC NONMISSION-ORIENTED LIFE SCIENCE RESEARCH OF THE PAST 40 YEARS WHOSE PAYOFFS WILL UNDOUBTEDLY AFFECT FAVORABLY FUTURE COST BENEFIT RATIOS.

ON THE BASIS OF SUCH INVESTMENT RETURNS ALONE, WE COULD CONFIDENTLY REST OUR CASE. THE MUSHKIN CONCLUSIONS ADD A DEGREE OF QUANTIFICATION TO THE "QUALITY OF LIFE" JUSTIFICATION FOR BIOMEDICAL RESEARCH.

BUT RECENT EVENTS HAVE HIGHLIGHTED OTHER BENEFICIAL AND MORE TANGIBLE EFFECTS OF THE NATIONAL INVESTMENT IN BIOMEDICAL RESEARCH. FOR EXAMPLE, IN THE PAST SIX OR SEVEN YEARS, A TOTALLY NEW INDUSTRY HAS EMERGED FROM THE UTILIZATION OF RECOMBINANT DNA AND HYBRIDOMA TECHNIQUES.

SUCH INDUSTRIAL TRANSLATIONS FROM BIOMEDICAL RESEARCH LABORATORIES ARE NOT UNIQUE TO THIS DECADE. INDUSTRIAL APPLICATIONS OF THE PROCESSES AND INCIDENTAL FINDINGS OF BIOMEDICAL RESEARCH DATE BACK MANY YEARS.

THE NIH OFFICE OF MEDICAL APPLICATIONS OF RESEARCH RECENTLY CONDUCTED A MODEST PILOT STUDY TO IDENTIFY DISCOVERIES IN BIOMEDICAL RESEARCH THAT HAVE BEEN ADOPTED BY INDUSTRY FOR COMMERCIAL APPLICATION OUTSIDE THE HEALTH CARE SECTOR. THEY FOUND INTERESTING AND IN SOME INSTANCES SURPRISING ROOTS OF TEN WELL-ESTABLISHED INDUSTRIAL PROCESSES OR PRODUCTS. FOR EXAMPLE:

- FREEZE DRYING WAS FIRST DEVELOPED IN BIOMEDICAL LABORATORIES FOR PRESERVING PROTEIN SOLUTIONS WITHOUT REFRIGERATION. SUBSEQUENTLY, FREEZE DRYING HAS BECOME A KEY PROCESS FOR FOOD PRESERVATION IN THE FOOD INDUSTRY.

- THE DEVELOPMENT OF FLEXIBLE ENDOSCOPES, IN PART SUPPORTED BY NIH GRANTS TO THE UNIVERSITY OF MICHIGAN, WAS A CRITICAL EVENT IN FIBER OPTIC TECHNOLOGY--NOW IN A LOGARITHMIC GROWTH PHASE WITH MAJOR APPLICATIONS IN TELECOMMUNICATIONS, INDUSTRIAL PROCESS CONTROLS, AND IN MILITARY APPLICATIONS. THE FIBER OPTICS MARKET IS EXPECTED TO INCREASE TO FOUR BILLION DOLLARS BY 1990 AND IS NOW IN THE RANGE OF A QUARTER BILLION.

- THE PILOT STUDY INCLUDED THE LABORATORY INSTRUMENT COMPUTER CALLED THE LINC--A FLEXIBLE AND POWERFUL

SCIENTIFIC TOOL DEVELOPED AT M.I.T. UNDER THE DIRECT SPONSORSHIP OF THE NIH IN COOPERATION WITH NASA. THE LINC NOT ONLY HAD AN IMPACT ON BIOMEDICAL RESEARCH BUT ALSO ON THE COMPUTER INDUSTRY. THE DIRECT DESCENDANTS OF LINC NOW ENJOY WORLDWIDE SALES OF OVER 2.5 BILLION ANNUALLY.

THE 10 EXAMPLES CITED IN THE STUDY OF BIOMEDICAL DISCOVERIES ADOPTED BY INDUSTRY FOR PURPOSES OTHER THAN HEALTH SERVICES WERE ESTIMATED TO PLAY A PART IN CONTRIBUTING ABOUT 37 BILLION ANNUALLY TO THE GROSS NATIONAL PRODUCT--AN AMOUNT THAT FOR COMPARISON EXCEEDS THE TOTAL COMBINED APPROPRIATIONS OF THE NIH SINCE ITS INCEPTION, AND IS MORE THAN 8 TIMES OUR CURRENT ANNUAL APPROPRIATION.

THE DEVELOPMENT OF RECOMBINANT DNA AND HYBRIDOMA TECHNIQUES PROVIDE THE MOST EXCITING CURRENT EXAMPLES OF THE CONTRIBUTION BIOMEDICAL RESEARCH CAN MAKE TO THE NATION'S ECONOMIC HEALTH WHILE AT THE SAME TIME OFFERING ENORMOUS POTENTIAL FOR IMPROVEMENTS IN THE PREVENTION, DIAGNOSIS, AND EFFECTIVE TREATMENT OF DISEASE.

THE MOST REMARKABLE ASPECT OF THIS BIOTECHNOLOGY IS ITS DIVERSE IMPACT. WE CAN CONFIDENTLY EXPECT TO HAVE A NEW SET OF PRODUCTS THAT ARE OF BIOLOGICAL ORIGIN AND ARE

EXQUISITELY SPECIFIC IN THEIR EFFECT. THIS MAY CHANGE OUR WHOLE APPROACH TO DRUG TREATMENT AND LEAD TO DRUGS WITH FEW SIDE EFFECTS BUT ENHANCED THERAPEUTIC IMPACT. IN OTHER AREAS, WE WILL USE BIOLOGICAL REACTIONS RATHER THAN STANDARD CHEMICAL PROCESSES TO CARRY OUT TASKS LIKE CLEANING UP OIL SPILLS AND TOXIC WASTES.

INDUSTRY WAS QUICK TO RECOGNIZE THE POTENTIAL OF THESE TECHNIQUES. AS OF 1983, 32 PUBLICLY OWNED COMPANIES WITH R&D ACTIVITIES OR PRODUCT LINES DIRECTLY RELATED TO THE NEW BIOTECHNOLOGY HAD BEEN ESTABLISHED. EQUITY INVESTMENT IN THESE COMPANIES TOTAL EIGHT HUNDRED THIRTEEN MILLION WITH AN ADDITIONAL ONE HUNDRED FORTY-EIGHT MILLION COMMITTED THROUGH RESEARCH AND DEVELOPMENT PARTNERSHIPS. OTHER MAJOR CORPORATIONS RANGING FROM CHEMICAL COMPANIES (MONSANTO, DUPONT) TO PHARMACEUTICAL HOUSES (ELI LILLY) AND FOOD PROCESSING COMPANIES (HEINZ, CAMPBELL) HAVE EITHER ESTABLISHED BIOTECHNOLOGY LABORATORIES OR NEGOTIATED AGREEMENTS WITH UNIVERSITIES TO CARRY OUT RESEARCH AND TO TRAIN INDUSTRY SCIENTISTS.

THIS EXPLOSIVE GROWTH OF INVESTMENT IS ALMOST UNPRECEDENTED, PARTICULARLY WHEN THE COMMERCIAL PROMISE OF BIOTECHNOLOGY HAS YET TO BE REALIZED. CLEARLY BOTH INVESTORS AND CORPORATE PLANNERS SEE ALMOST UNLIMITED POTENTIAL.

SINCE WORLD WAR II, THE FEDERAL GOVERNMENT HAS BEEN THE MAJOR SOURCE OF SUPPORT FOR BIOMEDICAL RESEARCH IN THIS COUNTRY. IN 1983, MORE THAN 52% OF ALL THE NATION'S BIOMEDICAL RESEARCH AND DEVELOPMENT WAS FEDERALLY CONDUCTED OR SUPPORTED.

THE PRINCIPAL MOTIVATION FOR GOVERNMENT INVOLVEMENT CONTINUES TO BE IMPROVEMENT OF THE HEALTH OF THE AMERICAN PEOPLE, BUT THERE IS GROWING RECOGNITION OF THE TANGIBLE ECONOMIC BENEFITS TO BE REALIZED FROM INVESTMENT IN RESEARCH. GEORGE KEYWORTH, THE PRESIDENT'S SCIENCE ADVISOR, HAS STATED THE GOVERNMENT'S POSITION THAT LONG-TERM U. S. ECONOMIC GROWTH REQUIRES BETTER USE OF RESEARCH AND DEVELOPMENT RESOURCES AND CLOSER INTERACTION OF THE ACADEMIC GOVERNMENT AND INDUSTRIAL RESEARCH COMMUNITIES. HE ADDED THAT "OUR CONCERN FOR INDUSTRIAL COMPETITIVENESS LED TO TODAY'S EMPHASES ON BASIC RESEARCH AND TRAINING OPPORTUNITIES."

IF OUR AIM IS TO MAINTAIN WORLD TECHNOLOGICAL LEADERSHIP OR IF IT IS TO BOOST THE NATIONAL ECONOMY OR IF IT IS TO IMPROVE THE HEALTH OF THE AMERICAN PEOPLE OR IF IT IS ANY MIX OF THESE GOALS, OUR COURSE OF ACTION IS CLEAR. WE NEED TO ASSURE ADEQUATE AND PREDICTABLE LEVELS OF SUPPORT FOR THE ENTIRE BIOMEDICAL RESEARCH ENTERPRISE. AT THE NIH, WE BELIEVE THE OPTIMAL LEVEL FOR PROGRESS WOULD MAKE IT POSSIBLE FOR THE AGENCY TO BE ABLE TO AWARD 45 TO

50 PERCENT OF APPROVED INDIVIDUAL APPLICATIONS FOR RESEARCH SUPPORT. IN THE CONTEXT OF THE FEDERAL BUDGET, THE SUMS NEEDED FOR THIS FACET OF OUR ACTIVITY ARE NOT LARGE. A YEAR AGO, WE ESTIMATED THAT WE WOULD NEED AN ADDITIONAL THREE TO FOUR HUNDRED MILLION DOLLARS PER YEAR FOR THREE YEARS WITH STEADY FUNDING FOR NEW AWARDS THEREAFTER. IT IS ENCOURAGING THAT THE INCREASE FOR 1984 APPROACHES THAT PROJECTION.

BUT IN DISCUSSING OUR ESSENTIAL NEEDS FOR RESEARCH SUPPORT, I WOULD INCLUDE AT THE MINIMUM ADEQUATE FUNDING FOR CENTERS, FOR CONTRACTS, FOR INTRAMURAL RESEARCH AND TRAINING, AS WELL AS FOR RESEARCH GRANTS.

ANOTHER MATTER REQUIRING ATTENTION FROM THE ENTIRE RESEARCH COMMUNITY AS WELL AS NIH IS THE NEED TO REPLACE OR PURCHASE THE INCREASINGLY SOPHISTICATED INSTRUMENTS REQUIRED FOR TODAY'S RESEARCH. WE HAVE ESTIMATED THAT 20 MILLION DOLLARS A YEAR FOR FIVE YEARS IS NEEDED FOR THE ACQUISITION OF LARGE-SCALE SHARED INSTRUMENTATION RESOURCES WITH ADDITIONAL FUNDS FOR THE PURCHASE THROUGH RESEARCH GRANTS OF SMALLER INSTRUMENTS. THE NIH HAS RECENTLY JOINED AN ONGOING STUDY BY THE NATIONAL SCIENCE FOUNDATION FOR THE PURPOSE OF SECURING A VALID CURRENT ASSESSMENT OF NATIONAL NEED.

FINALLY, EXTRAMURAL LABORATORIES AND FACILITIES ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND MORE RECENTLY BY THE NATIONAL EYE INSTITUTE, NIH STOPPED SUPPORTING FACILITIES AFTER 1969 AND CURRENTLY LACKS LEGAL AUTHORITY TO DO SO. AS A CONSEQUENCE, MANY OF THE FACILITIES BENEFITING FROM THE MAJOR NIH CONSTRUCTION EFFORT--THE HEALTH RESEARCH FACILITIES PROGRAM--ARE MORE THAN 20 YEARS OLD OR RAPIDLY APPROACHING THAT MARK.

AS IMPORTANT AS BUILDINGS AND ADEQUATE INSTRUMENTATION MAY BE, THERE IS ANOTHER CONSIDERATION OF EVEN GREATER MOMENT. I AM SPEAKING OF RESEARCH TRAINING. IN OUR VIEW, THE TRAINING AND RESEARCH PROGRAMS ARE SO CLOSELY INTER-WOVEN AS TO BE PRACTICALLY INDIVISIBLE, AND THE FUTURE OF THE RESEARCH ENTERPRISE IS TO A MAJOR DEGREE DETERMINED BY THE SUCCESS AND THE EFFECTIVENESS OF TODAY'S TRAINING PROGRAMS.

IN THIS CONTEXT, PERMIT ME TO QUOTE AN ARRESTING STATEMENT BY NOBELIST ARTHUR KORNBERG IN A SPEECH LAST YEAR ON BIOLOGY AND TECHNOLOGY. DR. KORNBERG SAID, "I AM CONFIDENT THAT WITHIN FIVE YEARS THE MOST EXCITING PROSPECTS FOR MEDICINE AND INDUSTRY WILL BE SUBJECTS AND PRODUCTS THAT NO ONE NOW EVEN TALKS ABOUT. WHICH

SCIENTISTS WILL BE SENSITIVE TO THESE NEW OPPORTUNITIES AND WHAT ORGANIZATIONS WILL BE EQUIPPED TO SEIZE THEM?"

HE WENT ON TO PREDICT "THE CURRENTLY ACTIVE SCIENTISTS WHO WILL LEAD THESE NEW ADVANCES ARE ALREADY BORED WITH CLONING AND SEQUENCING DNA AND MAKING HYBRIDOMAS. GIFTED YOUNG PEOPLE ENTERING BIOLOGIC SCIENCE WILL NOT JOIN THE CLONING PACK FOR HORMONES AND VACCINES BUT RATHER WILL DEVISE NEW TECHNIQUES TO SOLVE MORE CHALLENGING PROBLEMS."

IT IS HEARTENING THAT THE EXCITEMENT WE FEEL ABOUT THE VALUE AND POTENTIAL OF SCIENCE IS SPREADING IN EVER WIDENING CIRCLES IN THIS COUNTRY--THAT THE SOUNDNESS OF NATIONAL INVESTMENT IN BIOMEDICAL RESEARCH IS UNDERSTOOD--AND THAT ITS SPECTACULAR PAYOFFS ARE BEING RECOGNIZED.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

In the course of every year, the NIH receives many visitors from all parts of the world. Scientists, physicians, teachers, students, high officials of our Government, as well as from other countries -- and we do our best to make them feel welcome here. Today, we are pleased to have a visit from a leading Senator.

But, with it all, one group of guests on the NIH campus stands out above all others in importance. I am speaking, of course, of the patients who come to Bethesda and of their families -- of you.

You are more than guests. In a real sense, you are our colleagues in carrying out the vital and beneficial mission to which the National Institutes of Health is dedicated. You are members of the NIH community.

I am truly pleased to have this opportunity to join with the staff of the Clinical Center in extending to you as very special members of our family the warmest holiday greetings.

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*Holiday Concert, Clinical Center, December 15, 1983.

**Director, National Institutes of Health.

FEDERAL PROGRAMS OF TRAINING, RESEARCH, AND CLINICAL CARE IN ARTHRITIS*

BY

JAMES B. WYNGAARDEN, M.D.**

Many programs for the support of research training and clinical care in arthritis and related rheumatic diseases are supported by the Federal Government, state governments, and private groups, such as the Arthritis Foundation. The largest share of support for research on the causes, prevention, and control of arthritis is provided by the Federal Government through the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases at the National Institutes of Health. Within the NIH itself, 10 of the 11 Institutes and the Division of Research Resources are currently supporting research on arthritis and related musculoskeletal diseases at an annual rate of more than $80 million.

The NIADDK's 1984 research expenditures on arthritis will amount to about $60 million. The National Institute of Allergy and Infectious Diseases will spend more than $10 million on rheumatic diseases. In all, eight of our funding units each expect to exceed a million dollars in allocations for arthritis-related research this year.

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*Presented at the Annual Winter Symposium on Rheumatology, Snowmass, Colorado, January 20, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

The rate of growth in funding NIH's arthritis-related programs exceeds that experienced by all of our other major programs. Since 1980, arthritis research expenditures have increased by more than 50 percent, nearly twice as fast as the total NIH budget during the same period.

In the reports accompanying our 1984 appropriations, both the House and Senate Committees took special note of the fact that arthritis and musculoskeletal diseases affect more than 37 million of our citizens, and that a high percentage of our elderly population suffers from these diseases representing a substantial burden on the Medicare program as well as on Social Security disability insurance and Medicaid. The message from both sides of the Capitol was that more investigation is needed. In the words of the Senate report on the NIADDK appropriation, "The Committee believes that insufficient attention has been given to research on the more than 100 forms of arthritis and other musculoskeletal diseases, and therefore expects the Institute to significantly expand its research program on these diseases."

Another indication of the vitality of the arthritis program is the escalation in the numbers of applications for traditional investigator-initiated research project grants. In 1978, 97 such applications were received by the NIH and from them 30 new and competing awards were made. By 1983, the number of applications had doubled and 61 awards were made.

o Selection of interesting current projects and recent results.

o Multipurpose arthritis centers.

A. Selected research projects

B. Selected education projects

C. Selected community health services research projects.

OTHER AGENCIES

Another agency of the Federal Government, the Veterans Administration, is making major contributions both to research in the rheumatic diseases and to patient care for those with arthritis and related musculoskeletal diseases. The VA supports 172 medical centers, and 100 of these are affiliated with medical schools. Patient care required the expenditure by the VA in 1981 of $130 million for diseases of the musculoskeletal system and connective tissue. Among the veterans under VA care, 41,000 are disabled by arthritis, mostly by osteoarthritis and rheumatoid arthritis. Sixty-one rheumatology residents are centrally supported by the Veterans Administration's education and training component.

The Veterans Administration has devoted in recent years $138-$148 million in research and development in the following three areas: (1) medical research and demonstrations, (2) rehabilitation research and development, and (3) health services research. Its research budget in 1981 allowed for the support of 231 arthritis-related projects. There are rheumatic disease units of national stature at the Veterans Administration hospitals in Memphis, Oklahoma City, St. Louis, Buffalo, San Francisco, and Palo Alto. Investigators within these units are making major contributions in many areas of rheumatic disease research.

Two hospitals in the Veterans Administration system have been designated as rheumatology centers and, as such, have commanded extra resources and funding. The mission of these centers is to provide expert and exemplary specialized patient care for arthritis, to be an education resource in the rheumatic diseases, and to engage in basic investigations in rheumatology. The first of these centers was established at the Wood Hospital in Milwaukee, Wisconsin, where the major research emphasis is in the role of immune complexes in connective tissue diseases. The second center was established at the Philadelphia Veterans Administration Hospital under the direction of Dr. H. Ralph Schumacher.

Another Federal program is the development of regional centers for children with rheumatic diseases. This program grew out of discussions between the NIADDK and the Office of Maternal and Child Health of the Health Resources and Services Administration, aimed at improving interagency cooperation to help provide better services for children with arthritis. They planned for the establishment in several areas of the country regional centers for children and recommended that initially these centers should reside in locations where there is great competence and enthusiasm with respect to both pediatric rheumatology and the delivery of services to children at the state and local levels. The program was initiated in 1982 by the Office of Maternal and Child Health in collaboration with state agencies by establishing three juvenile arthritis centers in Philadelphia, Los Angeles, and Houston, with funding of $550,000 annually. During 1983, interest in this program escalated with 17 applications being

received and reviewed. Of these, 6 juvenile arthritis centers were funded, and they are located in Denver, Atlanta, Houston, Cincinnati, Honolulu, and Chicago. Current plans call for funding an additional 6 centers, a total of 12, in fiscal year 1984.

The research and training centers of the National Institute for Handicapped Research, a part of the Department of Education, conduct coordinated advanced programs in rehabilitation research and afford training to those engaged in research or provision of services. The arthritis training centers were mandated to investigate the efficacy of current physical modalities for impairment by arthritis and evaluate new approaches, and to develop strategies for functional assessment. The Secretary of Education announced his intention of funding at least two rehabilitation training centers concentrating on arthritis in an amount up to $725,000 each annually for up to five years. Two have been funded at levels of $600,000-$700,000 each. One at Tufts University has a special emphasis on children with rheumatic disease, and the other at the University of Virginia specializes in back diseases and impairments.

The Director of the Department of Education's National Institute for Handicapped Research also initiated in 1983 research fellowships in rehabilitation among various disciplines, and 17 fellowships were awarded. In addition, the Institute plans to initiate investigator-initiated research grants in fiscal year 1984, thus providing those interested in rheumatological rehabilitation opportunities for much needed investigations.

In reviewing the write-ups of recent research advances in arthritis, I was struck by the number of instances in which the use of animal models was central to the study. This reminded me of a matter which is of common concern and that I wish to discuss briefly with you.

The public pressure regarding research involving animals is familiar to all of you. I think we will all agree that biomedical research cannot continue to progress without the use of laboratory animals. While it is true that computer modeling and procedures in vitro may eventually replace animals in some toxicological testing, the involvement of animals to demonstrate the response of biological systems and organisms to carefully measured interventions is and will remain crucial to the research enterprise. Virtually every major medical advance in this century has depended upon animal experimentation. At the same time, of course, it is a moral imperative that animal experimentation be done in the most effective, conservative, and humane manner.

It is interesting that although the animal welfare policy of the Public Health Service is older than the formal policy for the protection of human subjects, the participation of humans in research is now rarely a matter of public conflict. We at NIH receive much more mail from the public regarding animal experimentation than on research involving human subjects. Looking to history for guidance, we might take a lesson from the policy making surrounding research on human subjects--perhaps we need a greater public forum on the subject of animals involved in

research. The human subjects protections now in place reflect a broad consensus of those concerned with the rights and welfare of human research subjects. On the other hand, the principles we follow for the use of animals reflect a consensus within the scientific community but they do not yet represent a consensus of those numerous groups and associations concerned with animal welfare. This is reflected in the fact that the 97th Congress has considered no fewer than five legislative initiatives concerning the use of animals in research. In addition, 23 states have pending legislation relating to animal research and testing and three congressional units are currently looking into various aspects of the use of laboratory animals.

The possible erosion of public support for our policies for humane care and use of laboratory animals is a matter of deep concern. The critics of our policies, some of whom are attacking biomedical research on animals as not only inhumane but unnecessary, appear to be sincere and politically sophisticated. It is therefore incumbent on us to strive to build a wider consensus concerning the policies for humane care and use of animals.

For its part, NIH has recently taken a number of actions and has future plans. We have completed site visits to institutions receiving support from NIH to conduct research that involves animals, one in each of the DHHS's ten regions selected at random. Although the site visit team found no evidence that animals were being utilized ineffectively or treated inhumanely, they did find some noncompliance with technicalities of NIH guidelines.

We are also in the process of having the Guide for the Use of Laboratory Animals updated for the fifth time, under contract with the National Academy of Sciences. The process included open hearings in Washington, San Francisco, and Chicago in order to gain comments from scientists and from the general public.

We also have firm plans to widen the public forum on the issue of animals involved in research. In the spring we plan to hold a national symposium at which the spectrum of views will be heard, designed to build a broad public consensus for appropriate policies for the use of animals in research. Starting next fall, NIH will begin a series of eight to nine regional workshops designed to promote better understanding and implementation of the PHS animal welfare policy by institutional animal care committees and administrators.

But the Federal Government cannot on its own adequately deal with the mounting pressures. It is the responsibility of the institutions and the investigators to become more active in responding to questions about the need for animals in research and appropriate safeguards. They should be familiar with the guidelines and policies, local and national, that apply; they should be willing to articulate the benefits that have accrued to medicine due to animal participation in research. Those who actually conduct research involving animals should be able to explain clearly to the public why the animals are absolutely necessary in the given experiment and why the experiment itself is important.

TRAINING

. Fellowships 1948
. TG's ~1955
. 1973 ~~Weinberger~~ - FOCUS

OUTCOMES - DAE
- Science Mag. ⊠ MD PhD

PI's in RO1/PO1 ⇓ MD

PI 10 yr. 9,000 → 17,000 MD — 300 ± /yr.
Trg 10,000; 3,800 ⇒ 1900 MDs — 300 — 1600
TG MD. ~10% PI's [? Other outcomes]

K series - Phys. Sci.

	TG's	24/36	2.5
	RF	18/54	
K	CI	14/30	
	RCDA	11/30	2.5
	New Awards	17/39	

NEW INST.

INTRODUCTORY REMARKS*

by

James B. Wyngaarden, M.D.**

Ladies and Gentlemen:

I'd like to welcome you this evening to the NIH Lecture. The NIH Lecture Series was established in 1953 to recognize outstanding scientific accomplishment and to contribute in a vital way to interchange of scientific information. We are pleased to have Dr. Frederic M. Richards, Professor of Molecular Biophysics at Yale University, with us tonight.

Dr. Richards' research interests have focused on problems relating to protein structure and function, including the definition of structure and activity of ribonuclease-S, and on theoretical studies of protein folding and protein-water interfaces.

He received his B.S. degree in chemistry from the Massachusetts Institute of technology, and his Ph.D. degree in biochemistry from Harvard University. In 1959 he joined the faculty of Yale University as an Assistant Professor of Biochemistry, becoming Professor in 1963 and Chairman of the Department of Molecular Biology and Biophysics. Since 1976 he has been the Director of the Jane Coffin Childs Memorial Fund for Medical Research.

Dr. Richards was a recipient of the Pfizer-Paul Lewis Award in Enzyme Chemistry and of the Kai Linderstrom-Lang Prize in Protein

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*NIH Lecture by Dr. Frederic M. Richards, Masur Auditorium, January 25, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

Chemistry. He has been a Guggenheim Fellow and received an honorary doctorate degree from the University of New Haven.

In 1971 Dr. Richards was elected to the National Academy of Sciences and also that same year became a Fellow of the American Academy of Arts and Sciences.

I'd like to remind you that a reception will be held for Dr. Richards on the first floor of the ACRF following tonight's lecture to which all of you are cordially invited.

The title of Dr. Richards' lecture tonight is: "Charge Distribution, Electrostatic Fields, and Enzyme Function."

Dr. Richards.

TALKING POINTS*

by

James B. Wyngaarden, M.D.**

I. Introductory remarks about the mission of NIH, its budget, partnership with medical schools and universities, mention of peer review system.

II. Justification of our investment in biomedical research.

A. Decreases in mortality and morbidity in heart disease and stroke. Dr. DeVita has probably talked about advances in cancer.

B. Economic benefits from biomedical research.

Actuarial estimates of the dollar value of lives saved and work years of sickness averted show that the ratio of total cumulative benefits to total cumulative research and development costs was between 10 to 1 and 16 to 1 for the 75-year period beginning in 1900. For the 45-year period beginning in 1930, the ratio was between 4 to 1 and 6 to 1. This lower but spectacular return reflects the high levels of basic, non-mission-oriented life science research of the past 40 years whose payoffs will affect favorably future cost benefit ratios. (From Mushkin study asking "Is the public getting an appropriate return for the multibillion dollar yearly expenditure in health research?")

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*"Current NIH Goals," Conference on Health Care: Economic and Ethical Issues, sponsored by The Washington Journalism Center, Watergate Hotel, January 26, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

A more tangible effect of our investment is the new growth in the past 6-7 years of a totally new industry--those based on recombinant DNA recombination and hybridoma techniques. This new biotechnology will change our whole approach to drug treatment, and will be applied to agriculture and animal husbandry as well as to environmental problems. As of 1983, 32 publicly owned companies with R & D activities or product lines directly related to the new biotechnology had been established. Equity investment totaled $813 million, with an additional $148 million committed through research and development partnerships.

C. NIH's role vis a vis university/industry partnerships: encouragement, but no direct participation by NIH; implement patent law changes, mainly support basic research and encourage "technology transfer" efforts; support training of new scientists. Other NIH ties to industry; small business innovation act, for-profit companies now competing for research grants along with non-profit institutions.

III. Discussion of areas that may be scientifically "ripe" for additional emphasis (as was done with cancer and heart disease earlier):
1) neurology and neurosciences research (nerve regeneration, advanced knowledge of how the brain works through scanning devices, the dementias); 2) tropical medicine research and vaccine development (dearth of vaccines now available, but DNA recombination should spur this on); and 3) arthritis (where bits of information are adding up to a better understanding of the various types of arthritis and their underlying causes).

In all three areas, personnel is trained and advanced methodologies are available. The payoffs would be great.

IV. Prevention activities to continue as important NIH emphasis area.

A. Chemoprevention research and education campaign to begin in 1984.

B. Osteoporosis - research and consensus conference.

C. Kidney disease - research and consensus conference on analgesic-caused kidney disease.

D. National high blood pressure education program to continue.

V. Issues confronting NIH and science this year:

A Rising costs of research/indirect costs.

B. Facilities and instrumentation outdated.

C. Growing public concern about animals in research.

d. Formation of new institutes.

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

The purpose of this pleasant occasion is to extend a warm welcome to Craig and Nancy Wallace as the newest members of the official family of the NIH. I am confident that the Wallaces already know how pleased we are to have them join us.

Although Craig's status as a full-time member of the NIH family is new, he is already well known to many of our scientists and program leaders through a long-time collaboration in research on infectious and tropical diseases. He was a member of the Bacteriology and Mycology Study Section from 1968 to 1972, serving as Chairman in the last year of his appointment to that committee. In November, just before coming here, while he was Commanding Officer of the Naval Medical Research Unit in Egypt, he served our interests as Chairman of the Subcommittee on Biomedical Research for the meeting of the U.S.-Egypt Joint Working Group on Health Cooperation. As you may remember, Secretary Heckler was a participant in that meeting.

A native of New Jersey, Dr. Wallace graduated from Princeton cum laude in 1950. After a year in the University of Virginia Law School, he saw the error of his ways and enrolled in the New York Medical College

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*Reception for Dr. Craig Wallace, new Director of the Fogarty International Center, at Stone House, February 1, 1984.

**Director, National Institutes of Health.

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from which he graduated in 1955, serving his internship and residency in internal medicine at Jefferson Medical College Hospital.

After spending three years at the Naval Medical Research Unit in Taipei as a clinical investigator, he joined the faculty of the Johns Hopkins School of Medicine in 1964, attaining the rank of Associate Professor of Medicine and of Pathobiology during his eight years with that institution. While at Hopkins he served for two years as resident coordinator of the University's Center for Medical Research and Training in Calcutta.

Dr. Wallace's military professional career in which he attained the rank of Captain included service in Ethiopia, in naval centers in Florida and California, as well as across the street with the Naval Medical Research and Development Command. His most recent assignment was in Egypt.

Dr. Wallace brings to the Fogarty International Center a special interest in international medical research, particularly in the area of tropical diseases. He is a member of numerous professional societies and has held many consultant appointments, particularly as a frequent advisor to the World Health Organization. In his dual capacity as Director of the Fogarty International Center and NIH Associate Director for International Research, he will provide leadership enhanced by his extensive experience abroad.

Craig, I suspect that your training in property law may come in handy when dealing with issues like space assignments.

We are delighted that Nancy and you have joined us.

TALKING POINTS*

by

James B. Wyngaarden, M.D.**

Dr. Pickett suggested some topics that the Council might be interested in:

- Dr. Pickett will have a "moment of silence" for Dr. Bill DeCesare and thought you might want to say something about him and his efforts in the GCRCs, which have contributed so much to nurturing clinical investigators and clinical investigation. (He very much appreciated the talk you gave at the Mt. Sinai 20th anniversary observance in October.)

- They would like to hear your views on the "sliding scale" proposal, having sent you a resolution on the matter in October (attached). Apparently they don't know that that proposal of last year has been laid to rest. There is a critical quantum of support below which many projects would become ineffective. Also, the mechanical application of a sliding scale principle would negate the considered judgment of study sections as to the essential components of proposed projects.

- If the President's 1985 budget has been released, they would like an overview from you.

- On stabilization--(Your AAMC speech will have appeared in the January 27 issue of Science. It covered your view on stabilization in some detail. They may want to refer to it). The so-called "stabilization strategy" was conceived to benefit the scientific enterprise. The first step toward effecting the stabilization concept was to apply it to research project grants, thus the 5,000 new and competing renewal research grants. But the present and continued adherence to the abridged stabilization strategy has become a problem because it does not reflect a broad view of the needs of biomedicine. But despite the untoward side effects of the partial implementation of a stabilization policy, the NIH has no desire to abandon the concept. Yet, essential mechanisms for research support include minimum adequate funding for centers, for contracts, for intramural research, and for training as well as for research grants. Another matter requiring attention is the need to replace or purchase the increasingly sophisticated instruments required for today's research. In addition, extramural laboratories and facilities are slowly deteriorating. Along these lines, DRR's program in instrumentation and interest in renovation and repair of animal research facilities will be important in maintaining the scientific enterprise.

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*National Advisory Research Resources Council Meeting, February 2, 1984.

**Director, National Institutes of Health.

- On training--the entire December 14 DAC meeting was devoted to manpower development programs. New data presented seem to indicate the importance of the length of training in contributing to the "success" of the programs. Many of the manpower development programs are accomplishing their goals--particularly the MSTP program for M.D./Ph.D.s, but there is concern about whether the training mechanism is the best way to go for M.D. investigators. National Advisory Councils of the BIDs have been asked to offer their ideas about the various training programs to be sure that we have the most advantageous "mix." Another difficult matter is that of stipends, since NIH's are well below roughly comparable programs. A committee of several BID Directors has been set up to make some recommendations on predoctoral and postdoctoral stipends in early spring.

- This year, major efforts are being made within NIH to focus on the problem of animals in research. Since DRR is a key institute in the matter, they might want a rundown on these activities:

  - It is important that NIH become more active in this area because it appears that public support for use of animals in research may be eroding. It is necessary to build a wider consensus concerning the policy for humane care and use of laboratory animals.

  - NIH has completed site visits to ten randomly selected institutions receiving support from NIH to conduct research that involves animals. The review has found that although the system of voluntary compliance works to promote the proper care and use of laboratory animals, some improvements can be made. The report should be available shortly.

  - The Guide to the Care and Use of Laboratory Animals is being updated and the PHS policy on animal welfare is also being revised. DRR is contributing to upgrading present conditions in major ways through the grants to improve animal facilties, for training specialists in laboratory animal science, and for controlling animal diseases through the diagnostic labs.

  - NIH also plans to widen the public forum on the issue of animals involved in research through a symposium in April designed to build a broad consensus for appropriate policies relating to the use of animals in research. Starting next fall, OPRR will begin a series of regional workshops designed to promote better understanding and implementation of the PHS animal welfare policy by institutional animal care committees and administrators.

- Finally, Dr. Pickett says the Council is "sour" on the SBIR and may ask questions about it. What can anyone say? We're stuck with it. In FY 1983, we spent $6.5 million on SBIR at 123 small companies. The Act specified that 0.2 percent of the extramural R&D budget be expended in FY 1983, 0.6 percent in FY 1984, 1.0 percent in FY 1985, and 1.25 percent in all subsequent years.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date October 31, 1983

From Director, Division of Research Resources, NIH

Subject Council Actions for the Attention of the Director, NIH

To Director, NIH
Through: Committee Management Officer, NIH Bonnie 11/1/83

There are two actions taken by the National Advisory Research Resources Council at its meeting on October 13-14, 1983, that I wish to bring to your attention.

First, Council unanimously opposes the "Sliding Scale" proposal for funding research grants and strongly recommends that full awards of investigator initiated grants be made to the extent possible with the funds available; further, Council encourages the Director, NIH to continue to seek mechanisms for additional funding.

The other action relates to an item brought to your attention in my memorandum of October 12, 1983 (Attachment I) in which I indicated application 2 P40 RR01293-04A1 from the University of Puerto Rico for support of the Caribbean Primate Center would be reviewed. Council assigned Low Program Relevance to the application and recommended it not be funded. Council also recommended interim support be provided via an administrative supplement to the current grant to allow submission of a revised application and/or a chance to secure alternative funding. A copy of the Staff Summary Statement of Recommended Council Action is attached for your information (Attachment II).

Betty H. Pickett

Betty H. Pickett, Ph.D.

Attachments (2)

cc: Dr. William Raub

11-1-83 To Dr Wyngaarden
through Dr Mahoney

DRAFT--1/5/84

TENTATIVE AGENDA
NATIONAL ADVISORY RESEARCH RESOURCES COUNCIL
February 2-3, 1984
Conf. Rm. 10, Bldg. 31-C
NIH, Bethesda, MD 20205

Thursday, Feb. 2
Open Session
9:00 a.m.

9:00-9:05 a.m.	I.	CALL TO ORDER. . . . . .Dr. Betty H. Pickett
9:05-9:20 a.m.	II.	COMMENTS BY DIRECTOR, NIH. . . . . .Dr. James B. Wyngaarden
9:20-9:30 a.m.	III.	CONSIDERATION OF MINUTES OF PREVIOUS MEETING (Mailed in Advance). . . . . .Dr. Betty H. Pickett
	IV.	CONSIDERATION OF FUTURE MEETING DATES. Dr. Betty H. Pickett
9:30-10:15 a.m.	V.	DISCUSSION OF THE REPORT OF THE DIRECTOR, DRR (Mailed in Advance) and BUDGET and LEGISLATIVE UPDATE . . . . . .Dr. Betty H. Pickett
10:15-10:30 a.m.		--COFFEE BREAK--
10:30-10:45 a.m.	VI.	REVIEW OF REVISED COUNCIL OPERATING PROCEDURES (Mailed in Advance) . . . .Dr. Betty H. Pickett
10:45-11:30 a.m.	VII.	REPORT ON NIH DIRECTOR'S ADVISORY COMMITTEE DISCUSSION ON TRAINING AND TRAINING RELATED PROGRAMS OF DRR. . . . . .Dr. Evelyn V. Hess Dr. James F. O'Donnell
11:30-12:00 Noon	VIII.	DISCUSSION OF DRR'S SPECIAL INSTRUMENTATION PROGRAMS--Biomedical Research Support--Dr. Thomas G. Bowery --Dr. Marjorie Tingle Minority Biomedical Research Support-- Dr. Ciriaco Q. Gonzales
12:00-1:30 p.m.		--LUNCH--
1:30-3:00 p.m.	IX.	PROGRAM WORK GROUP SESSIONS Animal Resources Program Work Group--Rm. 2A52 Biomedical Research Support Program Work Group--Rm. 8A28 Biotechnology Resources Program Work Group--Conf. Rm. 10 General Clinical Research Centers Program Work Group--Rm. 5B03 Minority Biomedical Research Support Program Work Group-- Conf. Rm. 3

Tentative Agenda
National Advisory Research Resources Council
February 2-3, 1984

3:00-3:15 p.m.		--COFFEE BREAK--
3:15-4:15 p.m.	X.	PROGRAM WORK GROUP REPORTS/COUNCIL DISCUSSION . . . . . .Dr. Betty H. Pickett and Work Groups
4:15-4:30 p.m.	XI.	PLANNING SUBCOMMITTEE REPORT . . . . .Dr. John J. Walsh
4:30 p.m.-Recess	XII.	NEW BUSINESS . . . . . .Dr. Betty H. Pickett

Friday, Feb. 3
8:30 a.m.-Adj.
Closed Session

XIII. CONSIDERATION OF APPLICATIONS . . . .Dr. James F. O'Donnell

8:30-9:00 a.m.	A.	Minority Biomedical Research Support Program-- Dr. Ciriaco Q. Gonzales & Staff
9:00-9:45 a.m.	B.	Biotechnology Resources Program-- Dr. Suzanne S. Stimler & Staff
9:45-10:15 a.m.	C.	General Clinical Research Centers Program-- Dr. James F. O'Donnell & Staff
10:15-10:30 a.m.		--COFFEE BREAK--
10:30-11:00 a.m.	D.	Animal Resources Program--Dr. William I. Gay & Staff

REMARKS*

by

James B. Wyngaarden, M.D.**

Thank you, Governor. I am very pleased to be here this evening and to participate in this occasion at which representatives of all the partners of the U.S. biomedical research enterprise have been gathered. Just five years ago, it was common for us in biomedical science to think of that partnership as including the Federal Government and the academic world. And, of course, the state governments, which have played an abiding role in support of the academic sector. Industry's involvement with academia in research has traditionally been modest, with its share of support at about three to four percent as compared with 78 percent from the Federal Government. It is just recently, since about 1978, that industry has become a strong factor in the biomedical coalition. The current rise of special arrangements between academia and industry to advance research and development is not, however, a radical departure. The "suddeness" of the appearance of new industry-academia relationships on the biomedical scene arises from the rapid accumulation of recent scientific discoveries with practical applications.

I think it bodes well for the future of the scientific enterprise, for the economic stability of the Nation, and for the health of all Americans, that three fine institutions of South Carolina have joined to honor two prestigious scientists and an eminent financier. This award celebration is recognition that in order to continue the momentum that has built up in biomedical research in the past five to ten years, we must depend upon many kinds of excellence and accomplishment.

In the not too distant past, it was common for the director of the NIH--in his regular duties of communicating with those interested in health research--to deliver talks almost exclusively at medical schools, professional scientific organizations, voluntary health organizations, and philanthropic foundations. That is still done, of course, but in the two years that I've been NIH Director, there have been increasing requests to speak to corporate groups, to journalists interested primarily in economics, and at national conferences relating to economic issues in health.

In the past, discussions, more often than not, concentrated on the input side of the enterprise--how to offer salaries that will attract and hold bright young investigators--how to afford the essential and usually expensive new instruments--where to find the money to keep a productive team together, and so forth. These are still important questions, but more

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*After dinner address, Drug Science Foundation Awards Dinner, Mills House Hotel, Charleston, SC, February 2, 1984.

**Director, National Institutes of Health, Bethesda, MD.

recently we have been called upon to turn to the output side. In the course of seeking funds to fuel the massive mechanism that biomedical research has become, we are constantly being asked to justify the substantial investment required. I enjoy the opportunity to make a case for research. It is also a responsibility we must accept.

The burden of our appeal and justification for support of biomedical research has emphasized quite properly the intangible and incalculable human benefits--the improvements in the quality of life--that have come from research. There can be no better reason for the current national investment of about $10 billion each year in biomedical research and development, $4 billion of which comes from the NIH.

But there is another effect of biomedical research--a benefit that is perhaps more evident to economists and planners in the audience than to those of us whose careers have been devoted to the biomedical sciences. A five-year study attempting to quantify the worth of biomedical research was conducted in the late 1970s and its results were published in 1979 in a book by Selma Mushkin, titled: "Biomedical Research: Costs and Benefits."[1] The study addressed the question, "Is the public getting an appropriate return for the multimillion dollar yearly expenditure on health research?"

The answer is an emphatic "yes." For example, the dollar values of lives saved and work years of sickness averted calculated as returns to the gross national product, balanced against the total cumulative research and development costs, yields a ratio of somewhere between 10-to-1 and 16-to-1 for the 75-year period beginning in 1900. For the 45-year period beginning in 1930, the ratio was between 4-to-1 and 6-to-1. The more recent lower, but still spectacular return, reflects the high levels of basic nonmission oriented life science research of the past 40 years whose payoffs will undoubtedly favorably affect future cost/benefit ratios.

In another analysis, this one published in 1983, Hugh Fudenberg estimated that taxpayers are currently saving $20-$30 yearly for each dollar spent 5-to-20 years ago on basic biomedical research in just one area--immunology. Clearly, biomedical research is an investment in the human condition, and it pays huge dividends.[2]

On the basis of such investment returns alone, we could confidently rest our case. The Mushkin conclusions add a degree of quantification to the "quality of life" argument for biomedical research. Whatever the cost of biomedical research, the price extracted for not funding it would be much greater.

But there remains a need to convince the public and its leaders that biomedical research is a blue chip national investment and the only hope for the U.S. to remain on the cutting edge of the biological and technological revolution. If it is not enough that biomedical research provides payoff in terms of lives saved and work years preserved, then perhaps an argument regarding nonmedical translations of biomedical research would help. Industrial applications of the processes and incidental findings of biomedical research date back many years.

The NIH recently conducted a modest pilot study to identify discoveries in biomedical research that have been adopted by industry for commercial application outside the health care sector. They found interesting, and in some instances, surprising roots of ten well-established industrial processes or products. For example:

- Freeze drying was first developed in biomedical laboratories for preserving protein solutions without refrigeration. Subsequently, freeze drying has become a key process for food preservation in the food industry.

- The development of flexible endoscopes, in part supported by NIH grants to the University of Michigan, was a critical event in fiber optic technology--now in a logarithmic growth phase with major applications in telecommunications, industrial process controls, and in military applications. The fiber optics market is expected to increase to four billion dollars by 1990 and is now in the range of a quarter billion.

- The pilot study included the laboratory instrument computer called the Linc--a flexible and powerful scientific tool developed at M.I.T. under the direct sponsorship of the NIH in cooperation with NASA. The Linc not only had an impact on biomedical research but also on the desk top computer industry. The direct descendants of Linc now enjoy worldwide sales of over $2.5 billion annually.

- The technique of immobilizing or forming water-insoluble derivatives of enzymes and other biologically active protein had its genesis in biomedical research. This constituted a major advance in research since these immobilized enzymes mimic the form of the enzyme in the living organism. The technique of immobilizing enzymes expanded beyond the bounds of medical and pharmaceutical applications to include analytical tools and food processing technologies--notably those used in making high fructose corn syrup and sugar beet molasses, and in the cheese industry. The value of the products based on enzyme immobilization is estimated at $2.1 billion.

- Finally, enzyme biochemistry, a field that has received significant contributions from biomedicine, has been applied to the production of beer, leather, and laundry detergents. In the production of beer, enzymatic chillproofing has been adopted as a standard treatment to deter turbidity and sediment formation. Application of enzyme biochemistry for the three industries totals $23.3 billion annually, $21.6 billion from beer making alone.

The 10 examples cited in the study of biomedical discoveries adopted by industry for purposes other than health services were estimated to play a part in contributing about $37 billion annually to the gross national product--an amount that for comparison exceeds the total combined appropriations of the NIH since its inception, and is more than eight times our current annual appropriation.

The development of recombinant DNA and hybridoma techniques provide the most exciting current examples of the contribution biomedical research can make to the Nation's economic health while at the same time offering enormous potential for improvements in the prevention, diagnosis, and effective treatment of disease.

The most remarkable aspect of this biotechnology is its diverse impact. We can confidently expect to have a new set of products that are of biological origin and are exquisitely specific in their effect. This may change our whole approach to drug treatment and lead to drugs with few side effects but enhanced therapeutic impact. In other areas, we will use biological reactions rather than standard chemical processes to carry out tasks like cleaning up oil spills and toxic wastes. Other applications are to be found in agriculture and food processing.

Industry was quick to recognize the potential of these techniques. Business Week[3] reports that by 1984 $2.5 billion had been invested in setting up more than 100 new companies dedicated to pioneering new products from biotechnology. Larger, more firmly established companies are also moving into this new area. In the pharmaceutical industry, biotechnology is causing a fundamental shift in the types of research and development being done. The Office of Technology Assessment estimates that at the turn of the century, annual sales of chemicals and drugs that are produced by gene splicing could top $15 billion.[4]

The tantalizing opportunities promised by the new biotechnology and the changing patterns of funding for biomedical research are the forces drawing the partners--industry-government-academia--together. We are faced with a richness of opportunity just at a time when flattening of Federal support of science seems to be a long-term reality. But if each member has something to offer to the partnership, then each also has much to gain.

In recent years, academic institutions have awakened to the commercial value of some of their activities. As Barbara Culliton of Science magazine put it, "For the first time, in basic biomedical research, the university has something extremely valuable to sell."[5] That commodity is very, very precious. It is excellence and creativity. The men and women working in science in universities and medical schools expand the frontiers in science. Industry, on the other hand, is rarely able to analyze carefully the developing edges of biology in relationship to the industry's particular product lines.[6] Yet, industry is beginning to realize that such neglect could have serious long-term consequences.

Returns to the academic institution, of course, include money for basic research, access to certain technologies, access to special facilities, and the availability for staff exchange and consultation.

Industry is interested in forming ties to academia not altruistically to make up for the Government's shortfall, but because it will help them succeed in their mission. Dr. Theodore Cooper,[7] a former NIH institute director, former Assistant Secretary for Health, and currently Executive Vice President of the Upjohn Co., has called the reasons the five P's: patents--to gain patentable ideas or entities; patients--to have access to

patients for clinical trials; publications--to have publications of clinical studies for use in securing FDA approval and as promotional aids; personnel--to attract scientists to the company as staff or consultants; and prestige--to have the prestige of association with academia's implied reliability and quality. All of these add up to the sixth "P"--profit.

In several ways, NIH is the "silent partner" in the partnership. Yet, a very vital partner. What can be overlooked in all the excitement about applying biotechnology is the solid foundation of basic research in the life science that undergirds these current efforts.[8] Research done in universities and medical schools around the country, most of it supported by the NIH, has moved from the use of simple model systems such as bacteria, to more complex ones such as human cells that could not be studied at the molecular level without recombinant DNA and hybridoma techniques. Basic scientists have made many new discoveries: genes that exist in pieces separated by nongene DNA; widespread existence of genes that jump from one position to another; genes that occur in multiple copies, various ones of which are activated at different times in development; genes that can multiply themselves when stimulated by factors in the environment; genes that can be picked up by viruses and can cause cancer when introduced into another cell. All of these basic discoveries and the methodologies by which they were discovered are the foundation of the new biotechnology and the preview of what is to come.

The bulk of support for basic biomedical research and training crucial to the development of biotechnology has come from NIH. In FY 1982, NIH extramural support for basic research directly related to biotechnology totaled $328 million or 12.1 percent of our extramural budget. Support for the underlying basic research totaled $841 million, or 31.1 percent. Estimates of expenditures for FY 1984 are approximately $400 million for directly related biotechnology research, and nearly $1 billion for the broader science base effort.

NIH's investment in the partnership goes further than the field of biotechnology. Total national support from health R & D in 1981 was an estimated $8.6 billion. Of that total, 39 percent was supported by NIH, 33 percent by industry, and 28 percent by other federal, state and local governments, and private nonprofit organizations. But when we look at all basic health research support, which totaled some $2.8 billion, 63 percent was provided by NIH and about 10 percent by industry.

Beyond its mandate to support research and training, NIH has another mission--a mission it shares with academia: the transfer of basic knowledge to benefit mankind. This technology transfer role is not always easy to accomplish without distracting from primary academic objectives and when federal dollars are stretched and priorities must be carefully set. Thus, both NIH and academia look to industry to share this function. It is both a responsibility and an opportunity.

Such partnerships, though, are not always so easy to foster. Several years ago, when new industry/academia ties in biotechnology were just beginning to be forged, a substantial level of concern was voiced over potential conflicts of interest and of loyalty under these new relationships, and of risks to the traditional basic values of the university. The concerns seem

to have abated, and academic institutions and industries have developed a number of different model relationships--such as the Drug Science Foundation. These promise to make maximum use of resources and strengths so that the partners can perform complementary roles in the advancement and application of biomedical knowledge.

It may even be that the triumvirate can combine forces to solve some important issues facing biomedical research today--for all three can benefit from their resolution. The importance of assuring a continuing supply of well-trained scientists is obvious to NIH, industry and the academic world. Training a cadre of able investigators is among the highest priorities of NIH. But industry, too, might contribute to continuity and expansion of the investigator pool by expanding its support of training in academic institutions.

Because of common interests, increased participation with academia and government in clinical trials should be attractive to industry. One thinks first of the pharmaceutical and other medical products industries in this connection. There is an urgent need to secure financial support--outside of government--in order to aid the transfer of valuable scientific advances into medical practice. This is especially true for the development and testing of "orphan drugs."

Another matter requiring attention from the entire research community is the need to replace or purchase the increasingly sophisticated instruments required for today's research. In addition, laboratories and facilities are slowly deteriorating and need remodeling or replacement. Another area that should concern all three partners in research is the erosion of public support for use of animals in research. All of us need to do whatever is possible to build a public acceptance for careful and controlled use of animals in research, lest our efforts to improve human health be irreparably stymied.

In summary, in an era of such great scientific opportunity, there is more than enough room for all three members of the government-industry-academia triangle to engage their full resources and energies. Moreover, this new era has just begun. Permit me to quote an arresting statement and question by Nobelist Arthur Kornberg in a speech last year on biology and technology.[9] He said, "I am confident that within five years the most exciting prospects for medicine and industry will be subjects and products that no one now even talks about. Which scientists," he asked," will be sensitive to these new opportunities and what organizations will be equipped to seize them?"

References

[1]Selma Mushkin, "Biomedical Research: Costs and Benefits," Ballinger Publishing Company, Cambridge, Mass., 1979.

[2]Hugh Fudenberg, "Basic Biomedical Research: A Cost Benefit Analysis in Biomedical Institutions, Biomedical Fundings, and Public Policy," edited by Hugh Fudenberg, Plenum Press, NY, 1983, p. 11.

[3]Business Week, January 23, 1984, pp. 84-94, "Biotech Comes of Age."

[4]As above.

[5]Culliton, B.J., "Biomedical Research Enters the Marketplace," New England Journal of Medicine, 304:1195-1201, 1981.

[6]Kenneth L. Melmon, "Changing Patterns of Biomedical Research Funding: The Impact on the Clinical Investigator," Clinical Research, Vol. 30, Number 3, September 1982, p. 310.

[7]Theodore Cooper, "Changing Patterns of Biomedical Research Funding: A View From Industry," Clinical Research, Vol. 30, Number 3, September 1982, p. 302.

[8]"Report on Biotechnology," prepared December 1983, Office of Program Planning and Evaluation, NIH.

[9]Arthur Kornberg, unpublished essay, "Biology and Technology," 1982.

THE PROCESS OF DETERMINING NECESSITY*

by

James B. Wyngaarden, M.D.**

My comments on the process of determining the necessity of using animals in particular research activities will be based on the policies and practices of the National Institutes of Health.

For background, permit me to describe the processes we apply to all research proposals in making decisions as to what projects should and can be supported.

More than two-thirds of the annual NIH budget of well over $4 billion is devoted to extramural grants for the support of research. Better than one-half of our total budget supports investigator-initiated projects. The project grants are made in response to applications submitted by individual scientists who describe in detail the research they wish to pursue and specify, insofar as is possible, the methodology they intend to apply to the problem. When grants are awarded, the grantee institution where the investigator is located assumes responsibility for stewardship of the funds providing assurance that the money will be used in accordance with the terms of the award.

Last year more than 23,000 applications were received and reviewed by various components of the NIH. Decisions were made on each of them, taking into account their scientific merit, their relevance to our program objectives, and the availability of funds.

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*Seminar on the Use of Animals in Biomedical Research, Cornell University Medical School, New York City, February 7, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

Because of the magnitude, diversity, and complexity of the NIH research mission and the desire to obtain the best advice possible, the NIH draws for assistance on the national pool of scientists actually engaged in research. Nearly 2,000 nonfederal scientists assist the NIH in the selection of the most meritorious research projects designed to implement biomedical research programs of the highest quality.

The NIH peer review system for research grant proposals is in essence two sequential levels of review. Both levels have statutory bases. The first level of review is performed by more than 100 scientific review groups that are established in general along the lines of scientific disciplines and consist of experts in relevant research fields.

The second level of review for research grant applications is performed by a National Advisory Board for each Bureau, Institute, or Division that supports extramural research.

Let me return for a moment, however, to the study sections and the other first-level scientific review groups. These panels of 12 to 20 members are composed primarily of nonfederal scientists selected by the NIH for their competence. As scientific leaders, they have broad knowledge of the status of research in their fields.

These groups review individual applications for their scientific merit and scientific significance including such considerations as (1) an assessment of the importance of the proposed research problem, (2) the novelty and originality of the approach, (3) the training, experience, and research competence or promise of the investigator or investigators, (4) the adequacy of the experimental design, (5) the suitability of the facilities, and (6) the appropriateness of the requested budget relative to the work proposed.

Recommendations of the scientific review groups are forwarded to the appropriate Bureau, Institute, or Division for the next level of review--that is, consideration by that unit's Council.

The second level of dual review for all grant proposals is the responsibility of the National Advisory Councils or Boards. By law, NIH can make grant awards only after they have been recommended by such Councils or Boards. These groups are comprised of both scientists and nonscientists and have broader responsibilites than the scientific review groups. The mix of members brings to bear on the grant review and award process knowledge in each of the relevant programmatic areas, familiarity with procedures, but also awareness of the roles of the diverse institutions in biomedical research, and of the health needs of the American people. The "lay" or public members of Councils add an important dimension to the final review process. The Councils and Boards also offer advice and make recommendations on policy and matters of significance to the mission and goals of the Bureaus, Institutes, and Divisions they serve.

Most research and development contract awards do not require Council approval, but program advisory committees composed largely of nongovernment experts play key roles in the development of solicitation for proposals. When solicited proposals are received, other technical review groups, again made up largely of outside advisors, are relied upon for critical evaluation and recommendations.

This is a general sketch of the review process by which the NIH assures itself of the appropriateness of the use of public funds in supporting proposed extramural research projects, and of the need for and merit of the research it supports.

The question has been asked, "Who is to decide if a particular research project is important enough to warrant the use of animals and who determines the most appropriate animal model?" For traditional NIH project grants, the short answer is that the initial decision as to the need for and the appropriate animal model for a specific project is made by the applicant-investigator. That decision, however, is subjected to repeated independent examination as the grant application makes its way through the NIH review process.

Before the application leaves the grantee institution, the principal research administrators, often with the advice of institutional review boards and animal care committees, must approve the proposal. Important considerations in that institutional review include the choice of the animal model, the number to be used, and the procedures proposed to make certain that the planned research can be carried out within the assurances that the institution has given the NIH regarding the care and use of research animals.

When any application for research involving vertebrates reaches the NIH, our study sections and other initial evaluation groups are required to critique (a) the appropriateness of the species of animals used, (b) the appropriateness of the number of animals used, (c) the care of animals before, during, and after experimental procedures, and (d) any other information that has significance for the care and treatment of animals.

If problems or questions regarding the proposed use of animals are identified, the review group flags the application for further consideration and judgment by the cognizant staff. If the review group is satisfied that the choice, care, and maintenance of the animals as proposed appear to be appropriate, a statement to that effect must also be included in the evaluation of the grant application. No award can be made unless the applicant institution has given the NIH Office for Protection from Research Risks an

acceptable assurance of compliance with the PHS Animal Welfare Policy and all questions raised by the initial review groups have been resolved to the satisfaction of the NIH.

INTRAMURAL

As you probably know, the NIH conducts a substantial amount of research in its intramural laboratories. Initial decisions as to the necessity for particular research projects are made by the investigators, subject to review by their laboratory chiefs, and under the general guidance of Scientific Directors. Each Bureau and Institute has one or more continuing Boards of Scientific Counselors that provide expert advice on the intramural scientific programs, making periodic visits to the laboratories for assessment of research in progress and evaluation of productivity and performance of staff scientists. Members of such Boards are selected from outside leaders in the basic and clinical sciences related to the research activities of the Bureau or Institute they advise.

Decisions as to the use of animals and the species and number required for specific projects are made first by the investigator, but are subjected to internal review that closely parallels that applied to extramural projects.

The Veterinary Resources Branch of the Division of Research Services provides professional and technical support services for NIH intramural programs and is responsible for production of defined research animals; the procurement, quarantine, conditioning, and issuance of animals from outside sources; management of a central animal surgery and radiology facility, animal disease diagnosis and control; and a range of consultative services.

The Branch is increasingly involved in activities to strengthen laboratory animal use and care programs both within the NIH and throughout the Federal Government. The Branch through the years has provided advice and

staff support for the Bureau, Institute, and Division animal care and research committees.

The NIH's direct involvement in large-scale testing programs is essentially limited to research on methodology. Small-scale screening of the efficacy of pharmacologic agents is carried out by a number of Institutes.

The National Institute of Environmental Health Sciences conducts a toxicology research and testing program for determining the toxic effects of chemicals to which people are exposed, and most importantly develops and validates more precise and less expensive methods for determining toxic effects. In the latter role, the NIEHS contributes significantly to the Department's National Toxicology Program, a multi-agency cooperative effort to develop the scientific information necessary to protect the American people from exposure to toxic chemicals.

The animal testing required by these programs is conducted by contract under rigid protocols developed by our scientists and advisors and is subject to the agency's standards for the use of animals. Virtually all such testing is carried out on various species and strains of rodents.

Permit me to address another question that comes up with some frequency. We are asked, "Is animal research repeated unnecessarily in some cases?"

We are keenly aware of the importance of and need for appropriate and careful use of animals in research. This is an issue to which the National Institutes of Health pays very close attention. It is important to distinguish between the frequently necessary and certainly valuable use of similar methodologies in research protocols and the unnecessary duplication of a protocol. The current peer review system is effective in assuring that unnecessary duplication of research does not occur. All applications for

research support from the Public Health Service must include as part of the research grant application a bibliography which lists relevant literature. This listing must be sufficiently comprehensive to demonstrate that the applicant is aware of current and past research in the area, has used that information as a basis for the proposed studies, and is not needlessly duplicating previous work. In addition, the applicant must include background discussion of the proposed research, an evaluation of relevant existing knowledge, and an explanation of information that will be gained from the project. All of this material is evaluated by reviewers. Furthermore, where warm-blooded animals are to be involved in a research protocol, reviewers evaluate specifically the need to use these animals. As part of their evaluation, the reviewers have the responsibility to make sure that both the number and species of animals are appropriate and that any animals involved in the research experience no unnecessary discomfort.

Further, the fact that we are able to fund only a little over one-third of meritorious research proposals is itself a powerful deterrent against unnecessary duplication and a safeguard against other than fully justified use of animals or other resources.

Let's step back for a moment from the details of procedures and consider the fundamental issue--namely, that biomedical research cannot continue to progress without the use of laboratory animals. While it is true that computer modeling and in vitro procedures may eventually reduce the number of animals used in some toxicological testing, the involvement of animals to demonstrate the response of biological systems and organisms to carefully measured interventions is and will remain central to the research enterprise.

Virtually every major medical advance in this century has depended upon animal experimentation, as shown by the progress against disorders such as

heart disease, cancer, kidney disease, hepatitis, and blindness. At the same time, of course, it is a moral imperative that animal experimentation be done in the most effective, conservative, and humane manner.

It is a matter of deep concern that public support for laboratory experiments involving animals may be eroding. The critics of Public Health Service policies--some of whom are attacking biomedical research on animals as not only inhumane but unnecessary--appear to be sincere and politically sophisticated. It is therefore incumbent on us to strive to build a wider consensus concerning the policy for human care and use of laboratory animals.

For its part, NIH has recently taken a number of actions and has additional plans.

NIH has completed site visits to ten randomly selected institutions receiving support from NIH to conduct research that involves animals. A report, to be completed soon, should help us further strengthen the system by which NIH assures that animals in research are adequately protected. It will also affect NIH future policy for the care and use of animals. The PHS Policy on Animal Welfare is now being revised, and a draft will soon be issued for public input.

NIH is also in the process of having its Guide updated for the fifth time, under contract with the National Academy of Sciences. The process included open hearings in Washington, San Francisco, and Chicago in order to gain comments from the scientists and the general public.

Because of its special concern for the health and well being of laboratory animals, NIH's Division of Research Resources continues to award a small number of grants for improvement of laboratory animal facilities, for training specialists in the laboratory animal field, and for controlling animal diseases through a series of diagnostic laboratories.

NIH has plans to widen the public forum on the issue of animals involved in research. This spring (April 11-12, NAS Auditorium, Washington, D.C.), we are scheduling a symposium designed to build a broad public consensus for appropriate policies relating to the use of animals in research. Starting next fall, NIH will begin a series of eight or nine regional workshops designed to promote better understanding and implementation of the PHS Policy on Animal Welfare by institutional animal care committees and administrators.

Also, the level of awareness about laboratory animals is very high on the part of our peer review advisors, and we can expect their continued vigilance, especially regarding duplication of efforts involving animals, the proposed use of too many animals in a given project, or the use of inappropriate animal models.

But the Federal Government cannot on its own adequately deal with the mounting pressure on this issue. It is the responsibility of the institutions and the investigators involved to become more active in responding to questions about the need for animals in research and appropriate safeguards. They should be familiar with the guidelines and policies, local and national, that apply; they should be willing to articulate the benefits that have accrued to medicine because of animal participation in research. Those who actually conduct research involving animals should be willing and able to explain clearly why a particular experiment is important and why animals are absolutely necessary in the given experiment.

CURRENT TRENDS OF NIH*

by

JAMES B. WYNGAARDEN, M.D.**

IN MID-FEBRUARY EACH YEAR, ALL FEDERAL AGENCIES BEGIN THEIR OBSERVANCE OF A SEASON NOT LISTED IN CALENDARS, RELIGIOUS OR SECULAR, A SPECIAL TIME NOT CELEBRATED IN SONG OR STORY. I REFER TO THE YEARLY BUDGET SEASON, HIGHLIGHTED BY THE ANNUAL ROUND OF HEARINGS BEFORE THE HOUSE AND SENATE APPROPRIATIONS COMMITTEES. THE RITUAL OBSERVANCES ARE PRESCRIBED BY THE CONSTITUTION, THE RULES OF CONGRESS AND BY LONG TRADITION. IN MODERN TIMES THEY HAVE REQUIRED THE PRODUCTION OF MASSIVE DOCUMENTATION REPORTING ACCOMPLISHMENTS AND JUSTIFYING REQUESTS. ALTHOUGH HIGHLY STYLIZED, THE HEARINGS PROCESS IS NOT STERILE--NOT BY ANY MEANS.

DURING THE HEARINGS, THE HEADS OF AGENCIES ARE CALLED UPON TO GIVE AN ACCOUNT OF STEWARDSHIP AND TO DEFEND THE PRESIDENT'S PROPOSALS FOR FUNDING THEIR ORGANIZATIONS DURING THE COMING FISCAL YEAR. IT HAS BEEN OUR EXPERIENCE THAT MEMBERS OF THE APPROPRIATIONS COMMITTEES AND THEIR STAFFS FOLLOW NIH ACTIVITIES CLOSELY AND FROM THEIR WORKING KNOWLEDGE OF OUR PROGRAMS, CAN BE EXPECTED TO ASK INCISIVE QUESTIONS--MOST OF WHICH WE WELCOME.

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*Faculty Meeting, University of Connecticut, Farmington, February 15, 1984.

**Director, National Institutes of Health, Bethesda, MD.

WE ARE SCHEDULED TO PRESENT OUR FY 1985 REQUEST TO THE HOUSE APPROPRIATIONS COMMITTEE IN EARLY MARCH, AND TO THE SENATE COMMITTEE IN EARLY APRIL, SO THE HEARINGS ARE MUCH ON OUR MINDS JUST NOW AT NIH.

THE FATE OF OUR BUDGET IS ALSO OF CONSIDERABLE CONCERN TO THE WHOLE OF THE ACADEMIC COMMUNITY, PARTICULARLY TO INSTITUTIONS SUCH AS THE UNIVERSITY OF CONNECTICUT THAT HAVE MAJOR COMMITMENTS TO BIOMEDICAL RESEARCH.

IN MY REMARKS TO THE APPROPRIATIONS COMMITTEES, I PLAN TO MAKE THE POINT THAT IN DISCUSSING THE NIH BUDGET, WE WILL BE ADDRESSING ISSUES THAT HAVE MUCH BROADER IMPLICATIONS THAN JUST THE ANNUAL OPERATING EXPENSES OF A GOVERNMENT AGENCY. OUR PRESENTATIONS INEVITABLY WILL ADDRESS CONCERNS OF THE NATION'S ENTIRE BIOMEDICAL RESEARCH ENTERPRISE. NIH PROGRAMS ARE THE SOURCE OF ABOUT 37 PERCENT OF THE OVERALL TOTAL OF PUBLIC AND PRIVATE FUNDS INVESTED IN HEALTH RELATED RESEARCH AND DEVELOPMENT IN THIS COUNTRY. OUR SHARE OF THE EXPENDITURES FOR BASIC BIOMEDICAL RESEARCH IS MUCH HIGHER. IT HAS BEEN ESTIMATED THAT NIH IS THE SOURCE OF 90 PERCENT OF THE SUPPORT USED BY UNIVERSITIES FOR SUCH FUNDAMENTAL INVESTIGATIONS.

FROM THE NIH PERSPECTIVE, IT WOULD BE DIFFICULT TO OVERESTIMATE THE IMPORTANCE WE ATTACH TO OUR PARTNERSHIP WITH ACADEMIA. FULLY 80 PERCENT OF THE $4,566,453,000 BEING REQUESTED FOR THE NIH NEXT YEAR IS ALLOCATED FOR GRANTS AND CONTRACTS TO SUPPORT RESEARCH AND TRAINING AT SOME 1200 LABORATORIES, CLINICS AND OTHER INSTITUTIONS. ACADEMIC INSTITUTIONS RECEIVE WELL OVER TWO-THIRDS OF THE TOTAL AMOUNT THAT NIH AWARDS IN GRANTS AND CONTRACTS EACH YEAR.

WE OFTEN SPEAK OF OUR RELATIONSHIP WITH ACADEMIC INSTITUTIONS AS A PARTNERSHIP, AND I FIND IT DIFFICULT TO IMPROVE ON THIS DESCRIPTION OF WHAT HAS BEEN A MUTUALLY BENEFICIAL RELATIONSHIP FOR MORE THAN 40 YEARS. THE MULTIPLE ADVANTAGES REALIZED FROM FEDERAL SUPPORT FOR THE CONDUCT OF RESEARCH AT ACADEMIC INSTITUTIONS WAS DEMONSTRATED CONCLUSIVELY DURING WORLD WAR II. IN THE SUCCEEDING YEARS, THE NIH/ACADEMIC PARTNERSHIP FOR BIOMEDICAL RESEARCH HAS BEEN EXTREMELY PRODUCTIVE. CERTAINLY WE HAVE MADE NO SECRET OF THE VALUE OF THESE COLLABORATIVE EFFORTS, BUT THE MEANS BY WHICH RESEARCH ADVANCES ARE MADE POSSIBLE SELDOM ARE REPORTED IN CONNECTION WITH HEADLINE NEWS ABOUT SCIENTIFIC ACCOMPLISHMENTS. FOR THAT REASON, WE WERE PARTICULARLY GRATIFIED WITH THE RESULTS OF A RECENT OPINION SURVEY CONDUCTED BY LOUIS HARRIS AND ASSOCIATES.

A SAMPLE OF MORE THAN 1200 LEADERS AND OTHER MEMBERS OF THE GENERAL PUBLIC WERE ASKED TO AGREE OR DISAGREE WITH THE STATEMENT:

"THE FEDERAL GOVERNMENT SHOULD INCREASE BY A SIZABLE AMOUNT THE MONEY THEY GIVE TO COLLEGES AND UNIVERSITIES FOR BASIC SCIENTIFIC AND TECHNOLOGICAL RESEARCH."

SIXTY-EIGHT PERCENT OF THE PERSONS INTERVIEWED AGREED WITH THAT STATEMENT, ONLY 28 PERCENT DISAGREED. EVEN A HIGHER PROPORTION (70 PERCENT) OF THAT PART OF THE SAMPLE MADE UP OF CONGRESSMEN AND THEIR TOP AIDES AGREED THAT THE FEDERAL CONTRIBUTION TO ACADEMIA FOR RESEARCH SHOULD BE INCREASED BY A SIZABLE AMOUNT. PERHAPS EVEN MORE SIGNIFICANT WAS THE PERCEPTION BY 64 PERCENT OF THE CONGRESSIONAL COHORT THAT THE GENERAL PUBLIC WOULD AGREE WITH SUCH INCREASES. IT IS OBVIOUS THAT WE WILL CALL THIS SURVEY TO THE ATTENTION OF THE APPROPRIATIONS COMMITTEES.

AS IMPORTANT AS SUBSTANTIAL FUNDING HAS BEEN AND CONTINUES TO BE FOR THE NURTURE OF THE BIOMEDICAL RESEARCH ENTERPRISE, THE MECHANISMS USED FOR PROVIDING SUCH SUPPORT HAVE PROVED TO BE THE KEY ELEMENTS IN MAKING THE MOST STRATEGIC USES OF AVAILABLE RESOURCES.

THE BACKBONE OF NIH EXTRAMURAL PROGRAMS IS THE INVESTIGATOR-INITIATED RESEARCH PROJECT. WELL OVER HALF (54.5 PERCENT) OF OUR TOTAL BUDGET REQUEST FOR 1985 IS ALLOCATED TO PROJECT GRANTS FOR THE SUPPORT OF THE RESEARCH

PROPOSED BY INDIVIDUAL INVESTIGATORS. IN THIS WAY, THE NIH, ACTING IN THE PUBLIC INTEREST, WILL CONTINUE TO DRAW UPON THE CREATIVITY OF THE ENTIRE AMERICAN SCIENTIFIC COMMUNITY. OUR CURRENT LEVEL OF FUNDING MAKES IT POSSIBLE FOR THE NIH TO FUND A LITTLE OVER ONE-THIRD OF THE PROPOSALS CONSIDERED TO BE WORTHY OF SUPPORT.

MEMBERS OF THE SCIENTIFIC COMMUNITY, ESPECIALLY THE FACULTY OF ACADEMIC MEDICAL CENTERS, ARE RELIED UPON IN LARGE MEASURE FOR ADVICE AS TO WHICH OF THE GRANT APPLICATIONS WE RECEIVE SHOULD BE GIVEN PRIORITY FOR FUNDING. THE DIFFICULT SELECTION PROCESS IS CARRIED OUT WITH THE ASSISTANCE OF SOME 2,000 NONFEDERAL SCIENTISTS WHO SERVE AS MEMBERS OF THE ESTABLISHED ADVISORY GROUPS THAT MAKE UP THE NIH PEER REVIEW SYSTEM.

GRANT APPLICATIONS UNDERGO REVIEW SEQUENTIALLY AT TWO DIFFERENT LEVELS. THE FIRST ASSESSMENT IS PERFORMED BY ONE OF THE MORE THAN 100 STUDY SECTIONS AND OTHER SCIENTIFIC REVIEW GROUPS ORGANIZED ALONG DISCIPLINARY LINES (FOR EXAMPLE, HEMATOLOGY, VIROLOGY, ETC.) AND CONSISTING OF EXPERTS IN SUCH AREAS.

THE SECOND LEVEL OF DUAL REVIEW IS PERFORMED BY THE FUNDING INSTITUTES' NATIONAL ADVISORY COUNCILS. THE COUNCILS

ARE COMPOSED OF SCIENTIFIC EXPERTS, AS WELL AS LEADERS IN FIELDS OTHER THAN SCIENCE. THE COUNCILS ASSESS THE APPLICATIONS FOR THEIR SCIENTIFIC MERIT, AS WELL AS FOR THEIR RELEVANCE TO THE INSTITUTES' MISSION AND THE NEED FOR SUCH RESEARCH. BY LAW ONLY THOSE GRANTS RECOMMENDED BY THE COUNCILS CAN BE AWARDED.

THUS, IN THE NIH REVIEW PROCESS AS WELL AS IN THE GENERATION OF RESEARCH IDEAS FOR NIH SUPPORT , THERE IS CONSTANT AND FOR THAT MATTER ESSENTIAL PARTICIPATION BY THE NATION'S SCIENTIFIC COMMUNITY.

THE UNIVERSITY OF CONNECTICUT IS WELL REPRESENTED ON A VARIETY OF NIH ADVISORY GROUPS. VICE PRESIDENT MULVIHILL IS A MEMBER OF OUR NATIONAL ADVISORY DENTAL RESEARCH COUNCIL AND PROFESSOR MARY OSBORNE IS A MEMBER OF OUR NATIONAL ADVISORY GENERAL MEDICAL SCIENCES COUNCIL. SIX OTHER SENIOR FACULTY MEMBERS FROM THIS CAMPUS AND SIX FROM THE STORRS CAMPUS ARE MEMBERS OF ESTABLISHED REVIEW COMMITTEES AND STUDY SECTIONS AT THE NIH.

IN ADDITION TO THE CONTRIBUTIONS THESE TALENTED INDIVIDUALS MAKE TO OUR PROGRAMS, I MUST ACKNOWLEDGE--AND ASK YOUR FORGIVENESS FOR--HAVING RECRUITED THE FORMER DEAN OF YOUR SCHOOL OF DENTAL MEDICINE. DR. HAROLD LÖE, WHO JUST OVER A YEAR AGO BECAME DIRECTOR OF THE NATIONAL INSTITUTE OF DENTAL RESEARCH, HAS BROUGHT TO OUR RESEARCH PROGRAMS THE PERSONAL QUALITIES OF VIGOR AND LEADERSHIP FOR WHICH HE WAS WELL KNOWN WHILE HERE IN FARMINGTON. AS ONE OF THE PRINCIPAL OFFICERS OF THE NIH, HIS VALUE TO OUR ORGANIZATION IN CARRYING OUT ITS IMPORTANT MISSION WAS QUICKLY RECOGNIZED.

A MOMENT AGO, I SPOKE OF OUR RELIANCE UPON THE INVESTIGATOR-INITIATED RESEARCH PROJECT AS THE PRIME MECHANISM FOR CARRYING OUT OUR MISSION.

EXPERIENCE OVER THE YEARS HAS CONVINCED US THAT THESE PROJECT GRANTS ARE ALSO EFFECTIVE INSTRUMENTS IN HELPING TO MAINTAIN THE VIGOR AND MOMENTUM OF THE AMERICAN BIOMEDICAL RESEARCH ENTERPRISE. THE CONTINUED AVAILABILITY OF A REASONABLY PREDICTABLE LEVEL OF SUPPORT OF SUCH GRANTS HAS SPECIAL MEANING FOR INDIVIDUAL MEMBERS OF THE RESEARCH

COMMUNITY, ESPECIALLY FOR YOUNG INVESTIGATORS BEGINNING THEIR RESEARCH CAREERS. TRENDS IN THE LEVELS ALLOCATED TO NEW AND COMPETING RENEWAL NIH GRANTS ARE WATCHED CLOSELY. FOR MANY THEY REPRESENT A KIND OF INDEX OF RESEARCH OPPORTUNITY.

THE 1985 BUDGET REQUEST FOR NIH CALLS FOR THE SUPPORT OF AN ESTIMATED 5,000 NEW AND COMPETING RESEARCH GRANTS. WHEN OUR CONTINUING COMMITMENTS TO NONCOMPETING AWARDS ARE ADDED TO THESE, THE TOTAL NUMBER OF RESEARCH AWARDS PREDICTED FOR 1985 WILL BE ABOVE 17,000. THE NIH AGGREGATE AVERAGE COST FOR NONCOMPETING CONTINUATION GRANTS WILL BE APPROXIMATELY FIVE PERCENT HIGHER THAN IN 1984. NEW AND COMPETING RESEARCH PROJECT GRANTS WILL ALSO RECEIVE AN AVERAGE COST INCREASE OF FIVE PERCENT OVER 1984.

AS YOU KNOW, THE GOAL OF FUNDING AT LEAST 5,000 NEW AND COMPETING AWARDS ATOP THE CONTINUING COMMITMENTS IS ONE FACET OF AN OVERALL STRATEGY--THE SO-CALLED STABILIZATION INITIATIVE--DESIGNED TO MEET THE NEED FOR LONG-TERM STABILITY IN THE FUNDING OF HEALTH RESEARCH. AS APPLIED TO RESEARCH PROJECT GRANTS--THE MOST IMPORTANT COMPONENT OF OUR ARRAY OF PROGRAMS--A MAJOR GOAL HAS BEEN TO MINIMIZE YEAR-TO-YEAR FLUCTUATIONS IN THE NUMBER OF NEW AND COMPETING RENEWAL GRANTS.

THE NIH HAS SUPPORTED AT LEAST 5,000 NEW AND COMPETING RENEWAL PROJECT GRANTS EACH YEAR SINCE 1980. IN 1984 THE TOTAL IS EXPECTED TO BE 5,272.

THE 1985 BUDGET PROPOSAL INCLUDES FULL FUNDING FOR INDIRECT COSTS. AS YOU PROBABLY KNOW, OUR BUDGET PROPOSALS FOR THE TWO PREVIOUS YEARS CALLED FOR PAYING ONLY 90 PERCENT OF INDIRECT COSTS. THE RESPONSE OF THE CONGRESS EACH YEAR WAS TO RESTORE THE 10 PERCENT REDUCTION. THE GROWTH OF INDIRECT COSTS AS A PERCENTAGE OF TOTAL COSTS CONTINUES TO BE A MATTER OF CONCERN. CURRENTLY, SUCH COSTS ARE RUNNING AT 31.1 PERCENT. AT THIS TIME, HOWEVER, NIH DOES NOT BELIEVE IT CAN TAKE ANY ACTION TO CONTAIN INDIRECT COSTS IN THE ABSENCE OF AN EQUITABLE GOVERNMENT-WIDE PLAN. NIH HAS OFFERED ITS ASSISTANCE TO THE PRESIDENT'S OFFICE OF SCIENCE AND TECHNOLOGY POLICY REGARDING THIS MATTER AND HAS SUBMITTED COMMENTS AND RECOMMENDATIONS TO THE CONGRESSIONAL GENERAL ACCOUNTING OFFICE IN CONNECTION WITH THE GAO'S RECENT ANALYSIS OF THE INDIRECT COST ISSUE. FULL INDIRECT COSTS WILL BE PAID ON NIH RESEARCH GRANTS IN 1984 AND 1985.

THE 1985 BUDGET REQUEST ALSO PROVIDES FOR THE SUPPORT OF 9,000 RESEARCH TRAINEES, A REDUCTION OF ABOUT 9 PERCENT FROM THE ESTIMATED 1984 LEVEL OF 9,863, BUT IT INCLUDES FUNDS FOR A 5 PERCENT INCREASE IN THE STIPEND LEVEL.

OVER THE PAST FIVE YEARS, THE NIH HAS SUPPORTED AN AVERAGE OF 10,600 TRAINEES PER YEAR, A NUMBER THAT REPRESENTS 98 PERCENT OF THE LEVEL RECOMMENDED BY THE NATIONAL ACADEMY OF SCIENCES. HOWEVER, THE TREND IS DOWNWARD. IN 1980, THE BUDGET FOR TRAINING WAS JUST OVER 5 PERCENT OF THE TOTAL NIH BUDGET. BY 1984, TRAINING'S SHARE OF THE BUDGET HAD BEEN REDUCED TO 3.7 PERCENT, AND THE 1985 SHARE OF THE REQUEST FOR TRAINING IS SLIGHTLY LOWER THAN LAST YEAR. THESE REDUCTIONS HAVE BEEN GOING ON AT A TIME WHEN OUR TOTAL BUDGET IS NOT INCREASING IN CURRENT DOLLARS.

AT THE DECEMBER MEETING OF THE NIH DIRECTOR'S ADVISORY COMMITTEE, IN WHICH JIM MULVIHILL PARTICIPATED, I ASKED THE COMMITTEE TO BEGIN CONSIDERING FOUR KEY QUESTIONS RELATED TO MANPOWER DEVELOPMENT. THESE QUESTIONS WERE ASKED IN THE CONTEXT OF OUR COMMON CONCERNS ABOUT THE NEED TO SUPPORT THE MOST PROMISING YOUNG PEOPLE WITH THE BEST POSSIBLE TRAINING MECHANISMS TO CARRY OUT RESEARCH MISSIONS IN THE YEARS TO COME.

WE FIRST ASKED, "WHAT ARE THE IMPLICATIONS OF TRENDS IN RESEARCH SUPPORT FOR MANPOWER DEVELOPMENT?" COROLLARY QUESTIONS ARE, "SHOULD THE SIZE OF OUR MANPOWER DEVELOPMENT PROGRAMS BE TIED TO OUR GUESSES ABOUT FUTURE LEVELS OF PUBLIC SUPPORT FOR HEALTH RESEARCH," AND "IS THERE AN OPTIMUM LEVEL OF INVESTMENT IN TRAINING?"

A SECOND QUESTION IS, "WHAT ARE THE FACTORS THAT ENTER INTO THE DETERMINATION OF NEED FOR TRAINING AND CAREER DEVELOPMENT?" AMONG THE FACTORS INVOLVED IS THE DEVELOPMENT OF NEW CLINICAL AND BASIC SCIENCE DISCIPLINES AND THEIR RELATIONSHIP TO CURRENT DISCIPLINES.

A THIRD QUESTION WE ASKED IS OF SPECIAL INTEREST TO THE INSTITUTIONS ENGAGED IN OUR TRAINING PROGRAMS, AS WELL AS TO THE NIH. WE ASKED, "WHAT ARE THE ELEMENTS THAT LEAD TO THE PRODUCTION OF SUCCESSFUL INVESTIGATORS?" OUR RESEARCH ENVIRONMENT IS BECOMING TECHNOLOGICALLY EVER MORE COMPLEX. ARE WE ENCOURAGING NEW CLINICAL INVESTIGATORS, FOR EXAMPLE, TO SEEK ENOUGH RESEARCH TRAINING AND EXPERIENCE IN THIS NEW ENVIRONMENT TO EXPECT THEM TO COMPETE SUCCESSFULLY IN OUR RESEARCH GRANT PROGRAM? SHOULD WE EXAMINE THE KIND OF TRAINING THEY ARE RECEIVING AND THE CHARACTERISTICS OF THE MOST EFFECTIVE TRAINING PROGRAMS?

AND FINALLY, WE ASKED THE ADVISORY COMMITTEE TO ADDRESS THE QUESTION OF A PROPER MIX OF MANPOWER DEVELOPMENT PROGRAMS. WE SUPPORT PREDOCTORAL STUDENTS, POSTDOCTORAL FELLOWS, AND TRAINEES. SOME MECHANISMS MAY BE SERVING OUR PURPOSES BETTER THAN OTHERS. SOME THAT WERE SUCCESSFUL 20 YEARS AGO MAY BE LESS SO TODAY.

WE HAD A FULL DISCUSSION OF THESE ISSUES AND, IT IS FAIR TO SAY, FROM THE EXCHANGES ALL OF US GAINED A BETTER UNDERSTANDING OF THE QUESTIONS. WE DID NOT EXPECT TO RESOLVE THEM. I PLAN TO DEVOTE A SUBSTANTIAL AMOUNT OF MY ATTENTION TO TRAINING IN THE COMING YEAR. AT THIS POINT, IT IS MY VIEW THAT NIH SUPPORT FOR PREDOCTORAL TRAINING FOR THE PH.D. CANDIDATE IS HIGHLY DESIRABLE AND SHOULD BE CONTINUED. I AM DISAPPOINTED IN THE RESPONSE OF MEDICAL STUDENTS TO THE NEW EQUIVALENT TO OUR POSTSOPHOMORE FELLOWSHIP. I THINK IT IS ESSENTIAL THAT YOUNG PEOPLE HAVE A CHANCE FOR GREATER EXPOSURE TO RESEARCH EARLY IN THEIR PROFESSIONAL TRAINING. WE WILL BE LOOKING FOR WAYS TO ATTRACT MORE STUDENTS INTO SUCH PROGRAMS.

FOR POSTDOCTORAL TRAINEES, THE INDICES OF SUCCESS OF PH.D.'S WHO HAVE BEEN ON TRAINING GRANTS OR FELLOWSHIPS ARE GOOD. OUR POSTDOCTORAL FELLOWSHIPS FOR M.D.S HAVE BEEN QUITE

PRODUCTIVE, BUT TRAINING GRANTS FOR M.D.S LESS SO. PROBLEMS INCLUDE THE LENGTH OF TRAINING, THE INTENSITY OF TRAINING, AND ITS ULTIMATE GOALS. ONE COMPLICATING FACTOR HERE IS THE RELATIONSHIP OF RESEARCH TRAINING TO THE SPECIALTY BOARD REQUIREMENTS. THIS PROGRAM WILL REQUIRE CAREFUL EXAMINATION.

OUR TWENTY-YEAR-OLD PROGRAM FOR COMBINED M.D./PH.D. STUDENTS, KNOWN AS THE MEDICAL SCIENTIST TRAINING PROGRAM, HAS BEEN QUITE SUCCESSFUL.

THE STIPEND ISSUE REMAINS A VEXING ONE, PARTICULARLY THE QUESTION OF WHAT SHOULD BE DONE ABOUT STIPENDS FOR PREDOCTORAL TRAINEES. ON ALL THESE MATTERS WE HAVE MORE DATA THAN INSIGHT AT THIS TIME.

PERMIT ME NOW TO TURN TO A SUBJECT THAT IS PRIMARILY AN NIH ORGANIZATIONAL MATTER, BUT AT THE SAME TIME IS AN ISSUE THAT HAS GENERATED A GREAT DEAL OF INTEREST IN THE EXTRAMURAL COMMUNITY. I WAS ASKED TO DISCUSS IT HERE. I SPEAK OF THE CURRENT STUDY OF THE ORGANIZATION OF THE NIH. LAST JUNE, WE ASKED THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES TO MAKE AN OBJECTIVE STUDY OF THE ORGANIZATIONAL STRUCTURE OF THE NIH AND, IN THE LIGHT OF SCIENTIFIC DEVELOPMENTS AND ECONOMIC CONDITIONS, TO RECOMMEND THE ESTABLISHMENT OF STANDARDS FOR DETERMINING THE NEED FOR ANY SUSTANTIAL

CHANGE IN THE STRUCTURE OF THE AGENCY. WE EXPECT THE STUDY TO BE COMPLETED AND TO HAVE A REPORT FROM THE IOM THIS NOVEMBER. WHEN THE STUDY WAS ANNOUNCED, THERE WAS SPECULATION IN SOME QUARTERS OF THE SCIENTIFIC COMMUNITY THAT OUR HIDDEN PURPOSE WAS TO FIND AN EXCUSE FOR DOING AWAY WITH OUR CATEGORICAL INSTITUTES--I CAN ASSURE YOU THAT THIS IS NOT TRUE.

THIS STUDY WAS REQUESTED AND IS BEING CONDUCTED AT A TIME WHEN THERE ARE INCREASING PRESSURES ON THE NIH FOR FRAGMENTATION THROUGH THE CREATION OF NEW ORGANIZATIONAL ENTITIES, EACH HAVING A RELATIVELY NARROW FOCUS ON A PARTICULAR SET OF HEALTH PROBLEMS. SUCH MOVEMENTS GAIN MUCH OF THEIR STRENGTH FROM AND INDEED ARE AN EXPRESSION OF THE PUBLIC'S CONFIDENCE IN THE POWER OF RESEARCH. THE MOVEMENTS ARE ALSO AN UNDERSTANDABLE REACTION BY SEGMENTS OF THE BIOMEDICAL COMMUNITY TO THE FUNDING CRUNCH AND REPRESENT AN EFFORT TO ESTABLISH ALTERED RESEARCH PRIORITIES THROUGH CONGRESSIONAL ACTION.

THERE IS A CERTAIN IRONY IN THIS SITUATION, FOR WITHIN SCIENCE ITSELF, THE TREND HAS BEEN TOWARD UNIFICATION RATHER THAN FRAGMENTATION. NOBEL LAUREATE ARTHUR KORNBERG RECENTLY SPOKE OF THE "CONFLUENCE OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SUBJECTS INTO A SINGLE UNIFIED DISCIPLINE."

HE OBSERVED, FOR EXAMPLE, THAT "ANATOMY, PHYSIOLOGY, BIO-CHEMISTRY, MICROBIOLOGY, IMMUNOLOGY, AND GENETICS HAVE NOW BEEN MERGED AND ARE EXPRESSED IN A COMMON LANGUAGE OF CHEMISTRY."

IN THE FACE OF THE PRESSURES FOR PROLIFERATION OF NEW SPECIALIZED PROGRAMS OR EVEN INSTITUTES, IT IS IMPORTANT TO REMEMBER, HOWEVER, THAT ADAMANT REFUSAL ON THE PART OF THE SCIENTIFIC AND ACADEMIC COMMUNITY TO CONSIDER CHANGE IS SHORT-SIGHTED. SUCH OPPOSITION IGNORES THE HISTORY OF THE DEVELOP-MENT OF THE NIH WHICH WAS INSTITUTE BY INSTITUTE AND MOST OF THESE NEW ORGANIZATIONAL ENTITIES WERE DISEASE-ORIENTED. FROM SUCH SPECIFICITY, PUBLIC INTEREST AND VIGOROUS SUPPORT WERE DRAWN.

A DOMINANT FACT IN ANY DISCUSSION OF BIOMEDICAL RESEARCH AT THIS TIME IS THE RECENT PACE OF DISCOVERY, ESPECIALLY IN THE REALM OF MOLECULAR BIOLOGY. EXPLOITATION OF OUR RAPIDLY EXPANDING KNOWLEDGE IN THIS FIELD IS OPENING NEW VISTAS FOR IMPROVEMENTS IN PREVENTION, DIAGNOSIS, AND TREATMENT OF MANY DISEASES. AND EVEN MORE EXCITING ARE THE TANTALIZING INSIGHTS GAINED FROM THE USE OF THE NEW TECHNIQUES IN THE STUDY OF DISORDERS RANGING FROM CANCER TO HUNTINGTON'S DISEASE.

JUST LAST WEEK, PUBLIC ANNOUNCEMENT WAS MADE THAT NIH SCIENTISTS WORKING WITH ITALIAN INVESTIGATORS HAVE IDENTIFIED A CRUCIAL MUTATION THAT TURNS THE POTENTIAL CANCER GENE PRESENT IN ALL CELLS INTO MALIGNANT ONCOGENES. THIS ADDITIONAL CONFIRMATION OF THE ONCOGENE THEORY OF CANCER'S ORIGIN BOLSTERS OUR CONFIDENCE THAT THIS LINE OF RESEARCH ON THE CAUSATION OF CANCER IS PROCEEDING IN A FRUITFUL DIRECTION.

DURING THE PAST YEAR, ONE OF OUR INTRAMURAL SCIENTISTS, DR. ROBERT GALLO, RECEIVED INTERNATIONAL RECOGNITION FOR HIS "REVOLUTIONARY DISCOVERY" OF THE FIRST VIRUS KNOWN TO BE ASSOCIATED WITH A HUMAN CANCER. DISCOVERY OF THE HUMAN T-CELL LEUKEMIA/LYMPHOMA VIRUS HAS OPENED A NEW REALM OF SCIENTIFIC INVESTIGATION WITH GREAT IMPLICATIONS FOR DIAGNOSING AND TREATING CERTAIN KINDS OF CANCER. ANOTHER IMPORTANT AREA OF PROGRESS MADE POSSIBLE BY RECOMBINANT DNA TECHNIQUES INVOLVES THE MODIFIDATION OF VACCINIA VIRUS--USED FOR 200 YEARS TO PRODUCE IMMUNITY TO SMALLPOX--SO THAT IT CAN CONFER PROTECTION AGAINST INFLUENZA AND HEPATITIS B. WORK WITH ANIMALS SUGGESTS THAT THE VACCINIA VIRUS CAN BE USED FOR SAFE, EFFECTIVE AND INEXPENSIVE VACCINES THAT CAN BE STORED AND ADMINISTERED EASILY. THESE WOULD PROTECT AGAINST A WIDE RANGE OF INFECTIOUS DISEASES.

THE RECENTLY DISCOVERED AND APPLIED TECHNIQUES IN MOLECULAR BIOLOGY HAVE BEEN RESPONSIBLE FOR SIGNIFICANT DEVELOPMENTS LEADING PRIMARILY TO THE IMPROVEMENT OF THE HEALTH AND WELL-BEING OF THE AMERICAN PEOPLE. AT THE SAME TIME, THEY HAVE LED TO THE CREATION OF TOTALLY NEW INDUSTRIES. RECENTLY, THE CONGRESSIONAL OFFICE OF TECHNOLOGY ASSESSMENT RELEASED A COMPREHENSIVE ANALYSIS OF COMMERCIAL BIOTECHNOLOGY. FROM ITS EXHAUSTIVE STUDY, THE OTA CONCLUDED THAT THE UNITED STATES HAS A COMMANDING LEAD WORLDWIDE IN THE DEVELOPMENT AND APPLICATION OF THE NEW BIOTECHNOLOGY. THE STUDY POINTED OUT THAT THE PRIVATE SECTOR IN THIS COUNTRY INVESTED MORE THAN A BILLION DOLLARS IN 1983 TO COMMERCIALIZE RECOMBINANT DNA, CELL FUSION, AND OTHER RELATED TECHNOLOGIES THAT WERE DEVELOPED WITH PUBLIC FUNDS DIRECTED TOWARD BIOMEDICAL RESEARCH. MOST OF THE BASIC RESEARCH LEADING TO THESE DEVELOPMENTS WAS CONDUCTED BY OR SUPPORTED THROUGH NIH.

I WILL CLOSE WITH ANOTHER QUOTATION FROM ARTHUR KORNBERG. ALTHOUGH HIS PICTURESQUE REMARK REFERRED SPECIFICALLY TO THE NEW BIOTECHNOLOGY, IT IS AT THE SAME TIME A TERSE DESCRIPTION OF THE CURRENT STATE OF THE BIOMEDICAL RESEARCH ENTERPRISE, AND A COMMENTARY ON OUR BUDGET ASPIRATIONS.

"MOLECULAR BIOLOGY," HE SAID, "HAS SUCCESSFULLY BROKEN INTO THE BANK OF CELLULAR CHEMISTRY, BUT FOR THE LACK OF BIO-MEDICAL TOOLS AND TRAINING IS STILL FUMBLING TO UNLOCK THE MAJOR VAULTS."

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TALKING POINTS*

for

James B. Wyngaarden, M.D.**

General Introduction

- NIH is the channel through which the Federal Government supports biomedical research in the United States. A multi-billion-dollar public investment through NIH has created in the United States the world's preeminent biomedical research capacity.

- The American biomedical research enterprise comprises a productive collaboration among government, academia, and industry. The system grew in response to challenges and opportunities; its achievements have contributed to better health for more people than ever before, and to the prospect of even greater health benefits.

- The truly national character of biomedical research in the United States is illustrated by these figures:

  -- An estimated 90 percent of basic biomedical research in the United States and more than 60 percent of research and development at American universities and medical schools is funded by NIH.

  -- Extramural awards in fiscal year 1982 accounted for 81 percent of the NIH budget of $3.6 billion (Slide 1) and 52 percent of awards went to medical schools (Slide 2).

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* NIAID 6th Annual Workshop for Minority Students, National 4-H Center, Chevy Chase, Maryland, February 28, 1984.

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History

- Origins of NIH (Slide 3) go back to the Laboratory of Hygiene established on Staten Island in 1887 -- (Slide 4) in a one-room laboratory. In 1891 it was moved to Service Headquarters in Washington, D.C. But the role of the Federal Government in biomedical research was minimal until World War II.

- The science of medicine developed slowly after the turn of the century, but it was not until 1935-45 that "modern medicine" had its beginning; the discovery of sulfonamides (1935) and penicillin (1940) increased the ability of physicians to intervene successfully in the control of disease (Modern Medicine).

- Concurrently, the Federal Government began to play a greater role and to conduct its own research:

  -- In 1930, (Slide 5) the Hygienic Laboratory was named the National Institute of Health.

  -- In 1937, the National Cancer Institute was established as a separate entity.

- Congress declared its belief in the importance of health research in the Public Helath Service Act of 1944. Section 301 serves as the keystone of our legislative structure by providing a perpetual authority for the conduct and support of biomedical research.

- The 1944 Act established the legislative basis (still valid today) for future developments. The Act provided for the association of the National Institute of Health with the National Cancer Institute.

- In 1948, Congress established the National Heart Institute, the National Institute of Dental Research, and the National Microbiological Institute, and changed the agency's name to the National Institutes of Health.

- After the war, NIH turned outward to the research community while expanding and strengthening its intramural base (Slide 6).

- In 1946, the Division of Research Grants was organized, laying the foundation for today's extensive extramural program, and, in 1953, the world-renowned Clinical Center was opened.

- By 1955, when Dr. James A. Shannon became director, the time was ripe for rapid and massive expansion of NIH and its programs, in organization and funding, and in the science base. The NIH budget was then $82 million; and, when Shannon retired in 1968, it had topped $1 billion. Dr. Shannon worked closely with Senator Lister Hill and Congressman John Fogarty to secure the support of the Congress. (1968: leveled off) (Slide 5) NIH/Convent.

- We are now confronted with an interesting paradox that derives directly from that earlier era. When the NIH budget was growing (Shannon Era), we had ample resources but a relative shortage of scientists and an inadequate knowledge base. We have built our scientific capability into a national resource; we have a cadre of skilled scientists; our knowledge is increasing exponentially; and our budget has been virtually level, in constant dollars, since 1974. It has increased in 1983 and 1984.

Organization

- (Slide 6) Today, NIH is organized into an Office of the Director, 3 research Bureaus, 8 research Institutes, 1 research Division, 3 service Divisions, and the National Library of Medicine (Slide 7).

  -- The organization also includes the Clinical Center, a combined research hospital and laboratory complex (ACRF), and the Fogarty International Center, which fosters international biomedical exchange.

  -- The 2 Bureaus and 5 Institutes focus on specific diseases: cancer; heart, lung and blood diseases; arthritis, diabetes and digestive and kidney diseases; neurological and communicative diseases and stroke; vision disorders; allergy and infectious diseases; and dental diseases.

  -- At 3 Institutes there is a more general health-related focus: on child health and human development, aging, and the relationship of human environment to health.

  -- The National Institute of General Medical Sciences focuses on increasing knowledge in the fundamental life sciences. The Division of Research Resources has responsibility for strengthening the institutional environment through support of a wide variety of essential research resources used by investigators.

Budgets and Trends

- Two major influences on present and future directions of NIH:

-- The explosive growth of biomedical knowledge offers greater opportunity for the prevention and treament of disease and disability than ever before.

-- The national economy demands restraint on Federal spending.

- Accordingly, NIH faces the question of how to maintain the incredible momentum of scientific discovery during a period of constrained resources.

- A look at the NIH budget during the past 25 years; main program growth during 1955-65 with continued increases into the 1970s.

- Consider the NIH budget in current and constant dollars between 1972 and 1983 (Slide 7):

  -- 15 percent increase in constant dollars, but growth of indirect costs almost exactly consumed this increment so funds for direct costs of research essentially the same in 1983 as in 1972.

  -- Peak year was 1979. Budget fell 12 percent in purchasing power between 1979 and 1982 and rose by 4 percent in 1983 and 6-7 in 1984; now it is -1 percent below 1979.

  -- Fiscal year 1984 budget for NIH is 4.3 billion! Thanks.

- Historically, we have accommodated to a relatively constant budget and an increasing number of excellent research proposals by shifting funds among mechanisms. These changes began in 1974 (Slide 8) but were not articulated as a policy until fiscal year 1980 when we asked Congress for sufficient funds to support 5,000 new and competing research grants and 10,000 trainees. Distortion of other mechanisms.

NIH Programs

- The typical (Slide 9) NIH Institute includes both an extramural and an intramural program component.

- Extramural programs are responsible for roughly 80 percent of NIH resources in research grants or contracts.

  -- Through these programs, NIH makes approximately 20,000 awards of various kinds to more than 1,200 institutions in every state and to several foreign countries; 21.5 percent.

  -- Concentration of resources in medical schools provides assurance that practical solutions of disease problems will receive appropriate priority in research activities.

  -- Grant applications receive two levels of review. The first, for scientific and technical merit, is done by groups of scientific experts who meet three times a year. The second, for program relevance, is done by Advisory Councils composed of both scientific experts and public members. Both elements of the review process are statutorily authorized. The system is more formal than that of the NSF which uses mail ballots to solicit opinions from scientists and relies heavily on judgment of agency staff in making awards.

- Nearly all Institutes have an intramural component of laboratory and clinical research programs.

  -- More than 2,500 research projects are in progress at all times, making NIH the largest center for biomedical and behavioral research in the world. One unique aspect of the research environment is the ability of scientists to concentrate on long-term efforts, such as the elucidation of the role of the slow viruses in neurologic diseases.

-- The intramural program support amounts to about 12 percent of the NIH budget. Only the most productive scientists receive permanent civil service status. These amount to less than 10 percent of the postdoctoral fellows who take advanced research training at NIH.

-- For most purposes, the intramural activities of the National Institute of Mental Health (NIMH) of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) associate closely with intramural NIH.

Training

- A high priority is attached to the training of the next generation of scientific investigators who are essential to the continued vigor of inquiry.

  -- New investigators fare well in the award process (50 percent of new awards and 10 percent of all awards go to first-time investigators). However, the majority of investigators are Ph.D.s (Slide 10).

- Of special concern is the present and future state of clinical research. A burgeoning of fundamental knowledge in the past decade has opened up vast opportunities for clinical research.

  -- However, a diminishing proportion of physicians are interested in applying themselves to the clinical research needs of tomorrow (Slide 12).

  -- We are considering initiatives to encourage M.D.s to enter or remain in research careers and to improve their effectiveness.

Conclusion and Summary

- NIH (Slide 13) adds up to more than the sum of its parts. Its roots are in the beginnings of modern medicine and its reach extends far into the future when the benefits of today's biomedical research will be enjoyed in better health for all.

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DECADES OF DISCOVERIES*

BY

JAMES B. WYNGAARDEN, M.D.**

I AM VERY HAPPY TO BE HERE IN ROCHESTER THIS EVENING TO CELEBRATE WITH YOU THE TENTH ANNIVERSARY OF THE UNIVERSITY OF ROCHESTER CANCER CENTER. THIS WILL BE THE LAST TRIP OUTSIDE OF THE NATIONAL INSTITUTES OF HEALTH FOR SOME TIME FOR ME AND MY INSTITUTE DIRECTOR COLLEAGUES, INCLUDING DR. DEVITA, DIRECTOR OF THE NATIONAL CANCER INSTITUTE, AND DR. FRANKLIN WILLIAMS, WHOM WE RECENTLY SPIRITED AWAY FROM ROCHESTER TO BE DIRECTOR OF THE NATIONAL INSTITUTE ON AGING. ALL OF US WILL BE QUARANTINED IN CONGRESSIONAL CHAMBERS FOR ABOUT A WEEK AND A HALF IN MARCH AND FOR ANOTHER WEEK IN APRIL. THE QUARANTINE HAS NOTHING TO DO WITH AN OUTBREAK OF "POTOMAC FEVER," HOWEVER. IT IS THAT TIME OF YEAR, MARKED BY NEITHER SECULAR NOR RELIGIOUS CALENDAR, WHEN ALL AGENCY HEADS APPEAR BEFORE THE HOUSE AND THEN THE SENATE APPROPRIATIONS COMMITTEES TO JUSTIFY THE PRESIDENT'S BUDGET REQUESTS (THIS TIME FOR FISCAL YEAR 1985) FOR THEIR AGENCIES.

NIH ASSOCIATION WITH INSTITUTIONS SUCH AS THE UNIVERSITY OF ROCHESTER MEDICAL CENTER AND THE ROCHESTER CANCER CENTER MAKE THE ANNUAL CONGRESSIONAL HEARINGS AS MUCH OF AN

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*After dinner address, Tenth Anniversary of the University of Rochester Cancer Center, March 1, 1984.

**Director, National Institutes of Health, Bethesda, MD.

OPPORTUNITY AS A CHALLENGE. WE APPEAR WITH CONFIDENCE BECAUSE THE STRENGTH OF THE NIH IN PART IS BASED ON THE EXCELLENCE AND ACCOMPLISHMENTS OF INSTITUTIONS SUCH AS THIS ONE. WHEN I, AND OTHER NIH OFFICIALS, APPEAR BEFORE THE APPROPRIATIONS COMMITTEES WE WILL MAKE IT VERY CLEAR THAT IN DISCUSSING THE NIH BUDGET, WE ARE ADDRESSING ISSUES THAT HAVE MUCH BROADER IMPLICATIONS THAN JUST THE ANNUAL OPERATING EXPENSES OF A GOVERNMENT AGENCY. OUR PRESENTATIONS INEVITABLY WILL ADDRESS THE FUTURE OF THE NATION'S ENTIRE BIOMEDICAL RESEARCH ENTERPRISE, AND THE ACCOMPLISHMENTS OF THIS CENTER, ALONE, MAKE A GOOD CASE FOR CONTINUED FUNDING FOR BIOMEDICAL RESEARCH.

AS WE CELEBRATE THIS TENTH ANNIVERSARY TODAY, WE ARE MARKING THE AWARD OF THE ORIGINAL NATIONAL CANCER INSTITUTE CORE GRANT TO THE CENTER IN 1974 AND DR. ROBERT COOPER'S LAUNCHING OF WHAT WOULD BE A STRONG, COMMUNITY-BASED RESEARCH AND TREATMENT FACILITY. BUT, OF COURSE, WE ARE REALLY LOOKING AT MUCH MORE. THE FOUNDATION OF THIS CANCER CENTER IS THE LONG TRADITION OF EXCELLENCE ESTABLISHED BY THE UNIVERSITY OF ROCHESTER MEDICAL CENTER. THE UNIVERSITY OF ROCHESTER MEDICAL CENTER, AS YOU ALL KNOW, SERVED AS A MODEL FOR SOME OF THE EARLIEST U.S. MEDICAL SCHOOLS. AND, IT ALSO HAS HAD A LONG PARTNERSHIP WITH THE NIH. TODAY, THE UNIVERSITY OF ROCHESTER MEDICAL CENTER RANKS AMONG THE TOP 20 MEDICAL SCHOOLS IN AMOUNT OF NIH FUNDS RECEIVED; IN FISCAL YEAR 1983, THAT WAS TOTAL OF 282 PROJECTS AT A LEVEL OF NEARLY $36 MILLION. ITS TRADITION OF DEDICATION TO TEACHING, RESEARCH AND PATIENT CARE MAINTAINS TODAY UNDER THE ABLE LEADERSHIP OF DR. SPROULL.

THERE IS NO DOUBT THAT THE MEDICAL CENTER AS A WHOLE AND THE CANCER CENTER ARE A MUTUALLY ENHANCING ENTERPRISE. THE OUTSTANDING REPUTATION OF THE MEDICAL CENTER CERTAINLY WAS INSTRUMENTAL IN DRAWING LEADING CANCER SPECIALISTS TO THE AREA DURING THE START-UP YEAR OF THE CANCER CENTER.

WHAT IS AN ANNIVERSARY FOR THE ROCHESTER CANCER CENTER IS A MILESTONE FOR THE NIH AND THE NCI AS WELL. IT DENOTES ADDITIONAL PROGRESS IN MEETING THE GOALS OF THE NATIONAL CANCER PROGRAM, LAUNCHED BY THE NATIONAL CANCER ACT OF 1971. ALTHOUGH ROCHESTER HELD SUBSTANTIAL NCI FUNDS FOR CANCER RESEARCH PRIOR TO 1971, THE CANCER CENTER, AS IT STANDS TODAY, WAS FORMED BY IMPETUS FROM THAT IMPORTANT LEGISLATION OF 1971 AND ITS 1974 AMENDMENTS.

THE NATIONAL CANCER PROGRAM WAS CREATED BECAUSE BOTH SCIENTISTS AND LAY PERSONS FELT, IN 1971, THAT WE HAD ACHIEVED A LEVEL OF UNDERSTANDING OF CANCER BIOLOGY AND MEDICINE SUCH THAT SUBSTANTIAL EXPANSION IN SUPPORT OF CANCER RESEARCH MIGHT PRODUCE A "CRITICAL MASS" OF SCIENTIFIC INFORMATION TO LAUNCH A NEW ERA. THE PROGRAM HAD TWO IMPORTANT FEATURES: FIRST, MARKEDLY EXPANDED SUPPORT FOR BASIC RESEARCH; AND SECOND, PROGRAM SUPPORT FOR THE APPLICATION OF THE RESULTS OF RESEARCH. THIS SECOND PORTION WAS A VERY IMPORTANT FEATURE OF THE PROGRAM, OFTEN OVERLOOKED BY THOSE NOT FAMILIAR WITH THE BREADTH OF THE LEGISLATIVE MANDATE. THE INTENT WAS TO GIVE THE NATIONAL CANCER INSTITUTE THE TOOLS TO APPLY THE RESULTS

OF BASIC RESEARCH AS THEY WERE DISCOVERED. THIS WAS THE "PEOPLE" PART OF THE NATIONAL CANCER PROGRAM AND THE CLEAR INTENT OF THE CONGRESS IN AN ERA WHEN CONGRESS WAS FAULTING THE NIH FOR NOT BEING AGGRESSIVE ENOUGH IN "TRANSLATING" THE FRUITS OF RESEARCH INTO THE PRACTICE OF MEDICINE.

THE NATIONAL CANCER PROGRAM HAS EVOLVED RAPIDLY SINCE THE PASSAGE OF THE ACT IN 1971:

IT PROVIDED TRAINING PROGRAMS IN RESEARCH AND CLINICAL MEDICINE THAT HAVE SEEDED THE COUNTRY WITH CANCER SPECIALISTS. USING FUNDS PROVIDED BY THE ACT, WE WENT FROM FEWER THAN 100 MEDICAL ONCOLOGISTS TO MORE THAN 3,000 TODAY; FROM A FEW HUNDRED RADIATION ONCOLOGISTS TO ABOUT 1,900 TODAY. NO DOUBT A GOOD NUMBER OF THEM TRAINED HERE AT THE ROCHESTER CANCER CENTER.

IT ALLOWED THE NCI TO ESTABLISH A PROGRAM TO CONTINUOUSLY MONITOR CANCER INCIDENCE AND SURVIVAL NATIONWIDE. THIS SO-CALLED SEER PROGRAM (FOR SURVEILLANCE, EPIDEMIOLOGY AND END-RESULTS) IS NECESSARY FOR TRACKING OUR PROGRESS AND SETTING NATIONAL GOALS.

IT ESTABLISHED A CANCER CONTROL PROGRAM--WHICH TODAY IS USING INFORMATION ON CANCER PREVENTION GENERATED IN THE PAST DECADE AND ADDRESSING THE PROBLEM OF CANCER PREVENTION IN A PROSPECTIVE WAY THROUGH CLEARLY DEFINED STAGES.

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IT EXPANDED OUR CLINICAL TRIALS PROGRAM TO STUDY NEW OR REVISED CANCER TREATMENTS. THIS PROGRAM--IN WHICH THIS CANCER CENTER HAS BEEN VERY ACTIVE--YIELDED MANY POSITIVE RESULTS NOW REFLECTED NATIONWIDE IN IMPROVED SURVIVAL AND DECREASED MORTALITY RATES FOR CANCER PATIENTS.

AND, OF COURSE, IT FOSTERED THE ESTABLISHMENT OF A NETWORK OF CANCER CENTERS--EACH SIMILAR TO THIS ONE--ACROSS THE COUNTRY. THEY ARE THE CENTERPIECES FOR GENERATING NEW IDEAS AND FOR APPLYING THE RESULTS OF BASIC RESEARCH TO BENEFIT PEOPLE.

THE ROCHESTER CANCER CENTER IS A MICROCOSM OF THE NATIONAL CANCER PROGRAM AT THE LOCAL LEVEL IN THAT IT COVERS THE CONTINUUM OF BIOMEDICAL RESEARCH--FROM BASIC SCIENCE TO APPLICATION. TOTAL NCI FUNDING AT THE CENTER WAS NEARLY $8 MILLION IN FISCAL YEAR 1983. THIS INCLUDED ABOUT 40 INVESTIGATOR-INITIATED AWARDS AT ALMOST $5 MILLION AND A MAJOR PROGRAM PROJECT GRANT FOR WORK IN RADIATION BIOLOGY AND THERAPY. CENTER STAFF HAVE ALSO COMPETED SUCCESSFULLY FOR AN INSTITUTIONAL TRAINING GRANT AND A CLINICAL CANCER EDUCATION PROGRAM GRANT--DESIGNED TO ENHANCE MEDICAL SCHOOL CURRICULA IN THE CANCER AREA. THE CENTER ALSO HAS FOUR NCI AWARDS IN CANCER CONTROL AND PREVENTION, SOME OF THESE AIMED AT COUNSELING PATIENTS AND AT THE PSYCHOSOCIAL ASPECTS OF CANCER AND ITS TREATMENT.

SCIENTISTS FROM THE CENTER HAVE BEEN INVOLVED FOR MANY YEARS WITH NCI-SUPPORTED CLINICAL TRIALS GROUPS: THE GYNECOLOGIC ONCOLOGY GROUP FOR 13 YEARS, THE EASTERN COOPERATIVE ONCOLOGY GROUP FOR 16 YEARS, AND THE RADIATION THERAPY ONCOLOGY GROUP FOR 12 YEARS. SUCH CLINICAL TRIALS BENEFIT NOT ONLY PATIENTS IN THE ROCHESTER AREA, BUT IN A VERY DIRECT WAY PATIENTS ALL OVER THE COUNTRY BECAUSE RESULTS OF THESE LARGE COOPERATIVE STUDIES GO FAR IN SHAPING THE STANDARD TREATMENTS OF TOMORROW.

THE ROCHESTER CANCER CENTER IS UNIQUE AMONG THE 54 NCI-SPONSORED CENTERS AROUND THE COUNTRY IN THAT IT IS MORE DEEPLY COMMUNITY BASED, WORKING NOT ONLY WITH THE MEDICAL CENTER HOSPITAL (STRONG MEMORIAL), BUT WITH A CONSORTIUM OF FOUR OTHER AREA HOSPITALS. THIS, NO DOUBT, HAS A VERY SALUTARY EFFECT UPON CANCER TREATMENT AND CARE IN THE ROCHESTER AREA--AN EFFECT THE COMMUNITY SHOULD BE PROUD OF. DR. COOPER'S EMPHASIS ON EXCELLENCE HAS A VERY OBVIOUS EFFECT ON THE QUALITY OF THE SCIENCE DONE AT THE CENTER IN THE CLINICAL AREAS AND IN THE BASIC SCIENCES--THE CENTER IS VERY STRONG IN MEDICAL ONCOLOGY AND RADIATION ONCOLOGY AND IN THE AREAS OF MOLECULAR BIOCHEMISTRY, CANCER PHARMACOLOGY, EXPERIMENTAL THERAPEUTICS, IMMUNOLOGY, AND ENDOCRINE CHEMISTRY.

THE CENTER'S REPUTATION IN THE CANCER SCIENCE COMMUNITY AND ITS SUCCESS IN COMPETING FOR NIH RESEARCH GRANTS ATTEST TO THAT EXCELLENCE. AND EXCELLENCE BEGETS DESERVED SUPPORT--THE CENTER'S CONTRIBUTIONS TO THE COMMUNITY HAVE BEEN RECOGNIZED

AND ALSO STIMULATED BY BENEFICENCE FROM MANY PRIVATE DONORS. I AM TOLD THAT ADDING TO CONSTRUCTION MONEY FROM NCI TO BUILD THE CENTER WAS A VERY GENEROUS CONTRIBUTION BY EASTMAN-KODAK IN THE NAME OF ITS EMPLOYEES.

THE SPECIAL EMPHASIS ON CANCER BY THE NATIONAL CANCER ACT--WHICH LED TO INCREASES IN CANCER SPENDING BY NCI FROM $232 MILLION IN 1971 TO $987 MILLION IN FISCAL YEAR 1984--HAS BEEN CONTROVERSIAL. THUS, THERE IS NO QUESTION THAT THE INFLUX OF MONEY INTO CANCER RESEARCH PAID OFF ON ALL FRONTS. THE EFFORT WORKED, IN PART BECAUSE THE BIOMEDICAL SCIENCE SURROUNDING CANCER QUESTIONS WAS "RIPE" FOR INCREASED EXPLORATION. AND, THERE WERE SUFFICIENT NUMBERS OF WELL-TRAINED INVESTIGATORS WHO COULD BE ATTRACTED INTO THE FIELD.

SOME WOULD DEBATE WHETHER OTHER BIOMEDICAL FIELDS OR DISCIPLINES WERE ADVERSELY AFFECTED BY THIS EMPHASIS ON CANCER RESEARCH AND CONTROL. I WOULD LIKE TO MAKE A FEW POINTS THAT ARE RELATED TO THIS QUESTION: FIRST, THE CANCER FIELD IS NOW SO PRODUCTIVE OF EXCITING NEW KNOWLEDGE, INSIGHTS, AND ADVANCES ALL ALONG THE CONTINUUM OF RESEARCH THAT WE MUST DO WHATEVER POSSIBLE TO MAINTAIN THE MOMENTUM THAT HAS BEEN GAINED THROUGH THE FIRST 13 YEARS OF THE NATIONAL CANCER PROGRAM. NO LESS THAN PEOPLE'S LIVES ARE AT STAKE. AND SECOND: EVEN IN THESE TIMES OF CONSTRAINED FEDERAL BUDGETS FOR RESEARCH, WE SHOULD NOT FAIL TO LOOK FOR <u>OTHER</u> AREAS IN BIOMEDICINE THAT MAY BE IN THE SAME RIPE STATE AS CANCER WAS A DECADE OR A DOZEN YEARS AGO. THESE COULD BE THE NEUROSCIENCES

WHERE WE HAVE ABOUT THE SAME LEVEL OF KNOWLEDGE AS WE HAD IN CANCER 10 YEARS AGO AND IN ADDITION SOME OF THE SCIENTIFIC TOOLS SUCH AS IMAGING DEVICES TO MAKE MAJOR INROADS IN KNOWLEDGE. IN THE FIELD OF TROPICAL MEDICINE WE HAVE A CORPS OF SCIENTISTS ARMED WITH ADVANCED BIOMEDICAL METHODOLOGIES AND PREPARED TO CONTRIBUTE IF SPECIAL EMPHASIS COULD BE GIVEN. THERE IS A GREAT NEED FOR CONTINUED EMPHASIS ON ARTHRITIS RESEARCH. HERE WE STILL SEEK SOME BASIC SCIENTIFIC CLUE THAT WILL SERVE AS A KEY TO UNRAVELING THIS MYSTERIOUS GROUP OF DISORDERS. THERE IS NO QUESTION THAT MANY BASIC ADVANCES MADE IN THE NAME OF CANCER--IN, FOR EXAMPLE, VIROLOGY AND IMMUNOLOGY--HAVE CONTRIBUTED ENORMOUSLY TO THESE AND OTHER DISEASE-RELATED STUDIES.

ALTHOUGH WE OFTEN SPEAK OF A "DECADE OF DISCOVERY" STEMMING FROM THE NATIONAL CANCER PROGRAM, IT IS DIFFICULT TO DATE RESEARCH ADVANCES FROM A SPECIFIC START POINT BECAUSE EACH RESEARCH ADVANCE IS BUILT UPON WHAT CAME BEFORE. SCIENTIFIC KNOWLEDGE IS CUMULATIVE, AND THE DISCOVERIES OF TODAY WILL FORM THE BASIS OF WHAT IS TO COME. YET FEW WOULD HESITATE TO CREDIT THE NATIONAL CANCER PROGRAM AND SUCH CENTERS AS THIS WITH TREMENDOUS MEASURABLE CLINICAL ADVANCES. ACCORDING TO FIGURES BASED ON SEER DATA, RELEASED BY THE NCI A FEW MONTHS AGO, 48 PERCENT OF ALL CANCER PATIENTS ARE CURABLE. DR. DEVITA BELIEVES, IN FACT, THAT ALTHOUGH THE DATA ARE NOT YET ALL IN, WE HAVE NOW PASSED THE 50 PERCENT CURABLE MARK. FOR A NUMBER OF MAJOR TYPES OF CANCER, MORE THAN TWO-THIRDS OF ALL PATIENTS ARE NOW CURABLE. SOME OF THE CANCERS WITH THE

MOST ENCOURAGING FIVE-YEAR RELATIVE SURVIVAL RATES ARE: THYROID, 92 PERCENT; ENDOMETRIUM, 87 PERCENT; TESTIS, 82 PERCENT; MELANOMA, 79 PERCENT; BLADDER, 72 PERCENT; PROSTATE, 67 PERCENT; UTERINE CERVIX, 67 PERCENT; FEMALE BREAST, 73 PERCENT; HODGKIN'S DISEASE, 70 PERCENT; AND LARYNX, 66 PERCENT. FOR WHITE CHILDREN UNDER AGE 15, DIAGNOSED BETWEEN 1973 AND 1980, THE SURVIVAL RATE IS 57 PERCENT FOR ALL CANCERS, UP FROM 54 PERCENT LAST YEAR.

MUCH OF THIS INCREASED SURVIVAL IS DUE TO IMPROVED THERAPY THROUGH CHEMOTHERAPY, SURGERY, AND RADIATION, SOMETIMES IN COMBINATION. MAJOR ACHIEVEMENTS HAVE BEEN MADE IN REDUCING THE UNTOWARD EFFECTS OF CANCER TREATMENTS: IN SOFT-TISSUE SARCOMA OF THE LIMB--THE STANDARD TREATMENT FOR WHICH HAS BEEN AMPUTATION--PHYSICIANS ARE NOW ABLE TO SAVE LIVES WITHOUT DRASTIC SURGERY. SURGERY FOR BREAST CANCER HAS BEEN MODIFIED--WITH HELP FROM PIONEERING STUDIES RIGHT HERE AT THE CANCER CENTER--SO THAT REMOVAL OF THE BREAST LUMP PLUS RADIATION IS NOW OFTEN POSSIBLE INSTEAD OF MASTECTOMY.

RECONSTRUCTION IS NOW BEING DONE FOLLOWING SURGERY FOR HEAD, NECK, AND BREAST TUMORS, AND THERE ARE EFFORTS TO DEVELOP LESS TOXIC DRUGS FOR CHEMOTHERAPY.

AND THERE ARE OTHER ADVANCES IN TREATMENT JUST ON THE HORIZON: SCIENTIST-PHYSICICANS ARE ATTEMPTING TO SENSITIZE TUMORS TO MAKE THEM MORE SUSCEPTIBLE TO THE EFFECTS OF RADIOTHERAPY; INVESTIGATORS AT SEVERAL LOCATIONS ARE STUDYING

THE BENEFITS OF APPLYING RADIOTHERAPY DURING SURGERY TO AVOID TOXICITY TO NORMAL TISSUES; AND STILL OTHER SCIENTISTS ARE WORKING TO APPLY THE NEW MONOCLONAL ANTIBODIES AND INTERFERON TO DETECT AND DESTROY CANCER CELLS.

MUCH OF THE PROGRESS WE SEE IN REDUCING CANCER MORTALITY AND MORBIDITY IS DUE TO THE COOPERATION AMONG MEMBERS OF THE MEDICAL COMMUNITY. BUILDING ON THE LONG-STANDING REFERRAL AND INFORMATION-SHARING TRADITIONS THAT CHARACTERIZE MEDICAL PRACTICE IN THIS COUNTRY, COMMUNITY PHYSICIANS AND SPECIALISTS HAVE WORKED TOGETHER TO PROVIDE THE CANCER PATIENT WITH THE BEST CHANCE OF SURVIVING HIS OR HER DISEASE. THIS KIND OF CLOSE COMMUNITY COOPERATION IS EVIDENT AT THE ROCHESTER CANCER CENTER, BUT ON A NATIONAL LEVEL THE NCI IS STRIVING TO SET ADDITIONAL MEANS AND WAYS TO MAKE THE NEWEST, MOST EFFECTIVE TREATMENTS MORE WIDELY AVAILABLE. THIS WAS A SPECIFIC MANDATE OF THE NATIONAL CANCER ACT.

ADDITIONAL GAINS CAN BE MADE IN TWO MAJOR WAYS: BY DEVELOPING NEW AND BETTER THERAPIES, AND BY ENCOURAGING WIDER APPLICATION OF THE BEST AND NEWEST THERAPIES. CLINICAL INVESTIGATORS AT ROCHESTER AND AROUND THE COUNTRY ARE WORKING ON BETTER TREATMENT--REFINING STANDARD METHODS OR COMING UP WITH ENTIRELY NEW APPROACHES. AND NCI IS ADDING TO THE NATIONAL CANCER PROGRAM NEW PROJECTS FOR TECHNOLOGY TRANSFER.

THE NATIONAL CANCER INSTITUTE HAS ESTIMATED THAT DESPITE THE INCREASING NUMBER OF CANCER CENTERS ACROSS THE COUNTRY OFFERING NEW THERAPIES, 80-85 PERCENT OF PATIENTS ARE TREATED IN THEIR HOME COMMUNITIES. BECAUSE CANCER REALLY REPRESENTS MORE THAN 100 DIFFERENT DISEASES, AND BECAUSE TREATMENT IS COMPLEX, SOPHISTICATED AND CONSTANTLY BEING REMODELED AND UPDATED, THERE IS A DANGER THAT MANY PATIENTS ARE NOT RECEIVING STATE-OF-THE-ART TREATMENT. SO NCI HAS COME UP WITH TWO NEW WAYS TO CLOSE THE GAP BETWEEN THE RESULTS ACHIEVED BY CANCER CENTERS AND WHAT IS ACHIEVED NATIONWIDE. THEY ARE BASED ON THE IDEA THAT TECHNOLOGY TRANSFER WILL TAKE PLACE ONLY IF PHYSICIANS TAKE PART IN THE DISCOVERY AND REMODELING OF CANCER TREATMENT.

LAST SUMMER, THE NCI BEGAN THE COMMUNITY CLINICAL ONCOLOGY PROGRAM (OR CCOP "SEE COPS"), TO AUGMENT AND SPREAD THE GOOD WORK BEING DONE IN CANCER CENTERS. THROUGH CCOPS, THE NCI IS FUNDING 62 GROUPS OF COMMUNITY PHYSICIANS TO PARTICIPATE IN CLINICAL RESEARCH. THESE 62 GROUPS--ONE OF WHICH IS AT ST. MARY'S HOSPITAL HERE IN ROCHESTER--WILL PARTICIPATE BY ENTERING A CERTAIN PERCENTAGE OF THEIR PATIENTS IN MAJOR CLINICAL TRIALS ATTEMPTING TO APPLY THE MOST RECENT FINDINGS OF BASIC RESEARCH. SUCH COOPERATIVE STUDIES WILL NOT ONLY BENEFIT LOCAL PATIENTS, BUT ALSO--BY INCREASING THE NUMBER OF PATIENTS IN TREATMENT STUDIES--WILL REDUCE THE TIME NEEDED TO FIND ANSWERS TO IMPORTANT QUESTIONS ABOUT NEW THERAPIES.

ANOTHER EFFORT TO CLOSE THE GAP IN INFORMATION ABOUT STATE-OF-THE-ARE TREATMENT IS NCI'S NEW PDQ OR PROTOCOL DATA QUERY SYSTEM. THIS IS A NATIONWIDE COMPUTERIZED INFORMATION SYSTEM OPERATED THROUGH THE NATIONAL LIBRARY OF MEDICINE'S MEDLARS SYSTEM, ALLOWING PHYSICIANS ALL OVER THE COUNTRY, WHEN FACED WITH A TREATMENT QUESTION, TO QUERY THE USER-FRIENDLY COMPUTER TO LEARN OF ACCEPTED STANDARD TREATMENT OPTIONS FOR SPECIFIC CANCERS; OF ON-GOING PROTOCOLS AT CANCER CENTERS; AND OF NAMES OF PHYSICIANS AND CENTERS INTERESTED AND EXPERIENCED IN THE MANAGEMENT OF SPECIFIC CANCERS. IT IS HOPED THAT THROUGH THESE ADDED PROGRAMS, THE NATIONAL STATISTICS FOR CANCER SURVIVAL WILL BEGIN TO REFLECT WHAT IS ACHIEVABLE IF OPTIMAL TREATMENT IS APPLIED NATIONWIDE.

I HAVE TALKED A GREAT DEAL ABOUT RESEARCH ADVANCES THAT ARE FULLY ENTRENCHED OR NOW ENTERING THE CLINICAL ARENA, BUT WE SHOULD REMEMBER THAT MOST OF THOSE ADVANCES ARE BASED UPON FUNDAMENTAL RESEARCH OF EARLIER YEARS. AND, IF WE ARE TO EXPERIENCE A SECOND "DECADE OF DISCOVERY," IT WILL BE DUE TO THE MASSIVE SUPPORT FOR BASIC RESEARCH--ONLY LITTLE LESS THAN HALF OF THE APPROXIMATELY $9 BILLION SPENT SINCE THE PASSAGE OF THE NATIONAL CANCER ACT. THE SUPPORT FOR BASIC STUDIES LAUNCHED THE CURRENT BIOLOGIC REVOLUTION. THE TECHNOLOGY WHICH, IN PART, EMERGED FROM THIS INVESTMENT INCLUDES: RESTRICTION ENZYMES, REVERSE TRANSCRIPTASE, RECOMBINANT DNA, DNA SEQUENCING; HYBRIDOMA TECHNOLOGY AND MONOCLONAL ANTIBODIES. JUST A FEW WEEKS AGO, FOR EXAMPLE, SCIENTISTS AT NCI IN

COLLABORATION WITH ITALIAN RESEARCHERS, IDENTIFIED THE CRUCIAL MUTATION--A CHANGE IN A SINGLE CHEMICAL MOLECULE--THAT TURNED A POTENTIAL CANCER GENE CANCEROUS IN A SMOKER'S LUNG. THIS ACHIEVEMENT CONFIRMS THE NEW "ONCOGENE" THERORY OF THE ORIGIN OF CANCER--THAT THESE SO-CALLED "ONCOGENES" ARE PROBABLY THE SWITCHES THAT MAKE NORMAL CELLS INTO CANCER CELLS, MOST LIKELY IN THE PRESENCE OF SOME OUTSIDE EVENT LIKE SMOKING, EXPOSURE TO RADIATION, OR TO SOME CHEMICAL. SUCH BRILLIANT ADVANCES HAVE REVOLUTIONIZED BIOLOGY, AND STUDIES OF ONCOGENES AND MANY, MANY OTHER BASIC INVESTIGATIONS ARE NOW LAYING THE FRAMEWORK FOR THE CLINICAL APPLICATIONS OF THE FUTURE.

I MENTIONED EARLIER THAT I AND OTHER NIH OFFICIALS WILL SOON ENTER CONGRESSIONAL HEARINGS REGARDING FUNDING FOR THE NEXT FISCAL YEAR FOR THE NIH AND ITS COMPONENTS. ALTHOUGH THE NIH BUDGET IS IN A STEADY STATE, NIH HAS RECEIVED STRONG SUPPORT FROM THE CONGRESS AND THE ADMINISTRATION AS COMPARED WITH OTHER AGENCIES IN THE HEALTH FIELD. MOREOVER, THERE IS AMPLE EVIDENCE OF GREAT STRENGTH IN THE PARTNERSHIP THAT MAKES UP THE BIOMEDICAL ENTERPRISE. THIS PARTNERSHIP--IN WHICH I WOULD INCLUDE THE NIH, THE BIOMEDICAL RESEARCH CENTERS AND UNIVERSITIES, THE STATE GOVERNMENTS AND PRIVATE INDUSTRIES--HAS ACCOMPLISHED A GREAT DEAL OVER THE YEARS IN SCIENCE AND IN MEDICINE. BUT THERE ARE SOME MUTUAL PROBLEMS THAT WILL REQUIRE THE ATTENTION OF ALL OF US IF RESEARCH IS TO CONTINUE: LABORATORIES AND FACILITIES AT INSTITUTIONS AROUND THE COUNTRY ARE SLOWLY DETERIORATING. WITH THE EXCEPTION OF FUNDS SUPPLIED BY THE CANCER PROGRAM AND THE NATIONAL EYE

INSTITUTE, NIH STOPPED SUPPORTING THE CONSTRUCTION OF RESEARCH FACILITIES AFTER 1969, AND CURRENTLY LACKS THE LEGAL AUTHORITY TO DO SO. AS A CONSEQUENCE, MANY OF THE FACILITIES BENEFITING FROM NIH'S PAST CONSTRUCTION EFFORTS ARE NOW MORE THAN 20 YEARS OLD OR RAPIDLY APPROACHING THAT MARK. ANOTHER MATTER DEMANDING ATTENTION IS THE NEED TO REPLACE OR PURCHASE THE INCREASINGLY SOPHISTICATED INSTRUMENTS REQUIRED FOR TODAY'S RESEARCH. AS IMPORTANT AS BUILDINGS AND FACILITIES MAY BE, THERE IS ANOTHER CONSIDERATION OF EVEN GREATER MOMENT. THIS SUBJECT IS NECESSARILY AT THE HEART OF ANY DISCUSSION ABOUT PRESERVING THE MOMENTUM OF DISCOVERY--THAT IS, RESEARCH TRAINING. IN OUR PLANS FOR THE FUTURE, ALL OF US IN THE PARTNERSHIP RECOGNIZE THAT TRAINING AND RESEARCH PROGRAMS ARE SO CLOSELY INTERWOVEN AS TO BE PRACTICALLY INDIVISIBLE. A SPECIAL AREA WHERE COOPERATION IS NEEDED IS IN THE USE OF ANIMALS IN RESEARCH. IT IS A MATTER OF DEEP CONCERN THAT PUBLIC SUPPORT FOR LABORATORY EXPERIMENTS INVOLVING ANIMALS MAY BE ERODING, ALTHOUGH EXPERIMENTATION WITH ANIMALS IS CLEARLY NECESSARY FOR THE FORESEEABLE FUTURE FOR CONTINUED RESEARCH PROGRESS. ALL MEMBERS OF THE PARTNERSHIP MUST PARTICIPATE IN APPROPRIATE WAYS SO THAT RESEARCH INVOLVING ANIMALS CAN CONTINUE TO IMPROVE HUMAN HEALTH.

IN CONCLUSION, I WANT TO CONGRATULATE THE ROCHESTER CANCER CENTER ON ITS FIRST DECADE OF DISCOVERY AND WISH YOU FUTURE DECADES OF DISCOVERIES. ALL OF YOU--PHYSICIANS, COMMUNITY LEADERS, STAFF MEMBERS, SCIENTIFIC INVESTIGATORS, AND STUDENTS--CAN BE PROUD OF WHAT THE CANCER CENTER HAS

ACHIEVED: EXAMPLES ABOUND TO DOCUMENT THE RELIEF FROM SUFFERING THAT HAS RESULTED FROM THE APPLICATION OF RESEARCH ADVANCES HERE. AND STUDENTS, FACULTY AND OTHERS CAN READILY APPRECIATE HOW THE CURIOSITY AND CRITICAL INQUIRY REQUIRED IN RESEARCH HAS ENHANCED THE TEACHING AND HEALTH CARE ENVIRONMENT HERE. THE AUDITORIUM OF THE NIH CLINICAL CENTER HAS A QUOTATION ENGRAVED IN THE MARBLE WALL AT ITS ENTRANCE--A QUOTE FROM ITS FIRST DIRECTOR, DR. JACK MASUR, THAT BEAUTIFULLY CAPTURES THE SPIRIT OF THIS CONCEPT: IT READS: "HOSPITALS WITH LONG TRADITIONS OF EXCELLENCE HAVE DEMONSTRATED ABUNDANTLY THAT RESEARCH ENHANCES THE VITALITY OF TEACHING; TEACHING LIFTS THE STANDARDS OF SERVICE; AND SERVICE OPENS NEW AVENUES OF INVESTIGATION." THESE SIMPLE TRUTHS HAVE BEEN BORNE OUT BY THE FIRST DECADE OF THE UNIVERSITY OF ROCHESTER CANCER CENTER.

March, 1984

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Institutes of Health

I welcome this opportunity to present testimony on the President's budget request for the National Institutes of Health for Fiscal Year 1985, to report briefly on the biomedical research enterprise in general, and to discuss some of its future potential.

Before proceeding to do so, however, I wish to express my thanks to you, Mr. Chairman, and to the Members of the Subcommittee, as well as the staff, for your continuing interest in and supportive concern for the progress of biomedical research and of the NIH in particular.

Substantial investment by the Federal Government in biomedical research for nearly four decades has resulted in America's unquestioned preeminence in this vital area of science. The establishment and growth of the Nation's productive biomedical research enterprise since World War II has been one of the most remarkable developments of that dynamic period.

Evidence of the vigor of American biomedical research is apparent in every facet of that enterprise. An outstanding example was highlighted by the Congressional Office of Technology Assessment in its recently released analysis of commercial biotechnology. From its exhaustive study, the OTA concluded that the United States has a commanding lead worldwide in the development and application of the new biotechnology. The study pointed out that the private sector in this country invested more than $1 billion in 1983 to commercialize recombinant DNA, cell fusion and other related technologies that were developed with public funds directed toward biomedical research. Most of the basic research that led to these developments was conducted by or supported through NIH.

Consequently, in discussing the plans and budget proposals for the NIH, we are addressing broader concerns than the support of a Federal agency as such. Nearly 60 percent of all health-related research and development in America's universities and medical schools is funded through the NIH. Four-fifths of the NIH budget is expended through extramural awards for the support of non-Federal investigators and public and private institutions engaged in biomedical research. These researchers, together with the investigators performing research in the NIH intramural laboratories and clinics, form a substantial element of the American biomedical research community and have been responsible for significant developments leading primarily to the improvement of the health and well-being of the American people, and secondarily to the creation of totally new industries.

Dissemination of the results of NIH-funded research, both to the general public and to the biomedical community, is a key element in the improvement of the Nation's health. Computerized information retrieval systems based at NIH are used millions of times each year to provide vital information to practitioners, scientists, and educators around the United States.

The findings of an opinion survey conducted late last year by Louis Harris and Associates reflect widespread public awareness of the productivity of the Federal/academic partnership for research--and this partnership is the key element of the programs of the NIH. Sixty-eight percent of the persons surveyed approved the award of funds by the Federal Government to colleges and universities for basic science and technological research.

Any overview of the Nation's scientific enterprise should also take special note of the NIH intramural research program that continues to play a key role in the biomedical research effort. The unique expertise and facilities at NIH offer opportunities for conducting certain kinds of research that cannot be duplicated elsewhere. The intramural program's flexibility made it possible to focus the attention of experts in many disciplines on the devastating Acquired Immune Deficiency Syndrome just as the disease was being recognized in mid-1981.

Although finding conclusively the cause of AIDS and the development of effective prevention and treatment measures has proved to be exceedingly difficult, there can be no doubt that the solution is nearer than it would have been in the absence of the fundamental knowledge gained in basic research on immunology over a period of years.

In the testimony to follow from each of the major NIH components, recent research accomplishments and promising developments will be presented in some detail, but I will take the liberty at this time of highlighting a few of them.

- Positron emission tomography (PET) continues to reveal more information that is helping us to understand and, in some cases, to treat a wide range of disorders. This imaging device enables scientists to observe directly the living brain as it functions. PET research conducted and supported by the NIH has already yielded new information about epilepsy, schizophrenia, and Alzheimer's disease. The medical opportunities provided by this technology have only begun to be explored.

- In mid-January, NIH announced the results of a 10-year clinical trial in 4,000 men that provided the first conclusive evidence that lowering cholesterol levels in the blood stream can reduce the rate of heart attacks. Middle aged men in the study, who were healthy except for elevated blood cholesterol, reduced their risk of death from heart attack by 24 percent and their risk of nonfatal heart attack by 19 percent by taking a cholesterol-lowering drug. Heart disease is the number one killer in this country, and an estimated 30 million Americans have elevated blood levels of cholesterol.

- Survival rates for cancer patients continue to improve. These successes are due, in large part, to research advances in radiation therapy, chemotherapy, and surgery. During the past year, an intramural scientist, Dr. Robert Gallo, has been internationally recognized for his

discovery of the first virus known to be associated with a human cancer. Discovery of that virus, called HTLV or human T-cell leukemia/lymphoma virus, has opened a realm of scientific inquiry with great implications for diagnosing and treating certain kinds of cancers. HTLV has recently been identified by NIH scientists as related to AIDS and is one of the many leads being following in the search for more information about this disease.

- Exploitation of our rapidly expanding knowledge of molecular biology is opening new vistas for improvements in prevention, diagnosis, and treatment of many diseases. Few medical tools are as versatile as hybridomas--created by the fusion of a cancer cell with a normal antibody producing cell. These hybrid cells have the unique ability to make unlimited amounts of specific antibodies--a major component of the body's "search and destroy" mechanism against cancers and viruses. I should note that although hybridomas were first produced in England nine years ago, it is fair to say that this would not have been possible without the outstanding research of an NIH intramural scientist, Dr. Michael Potter, who created the system of plasma cell tumors that are used to produce hybridomas.

- Monoclonal antibodies are now being produced in large quantities for use in NIH-supported clinical trials in patients with leukemia and lymphoma. Most scientists agree that we have only begun to realize the potential of monoclonal antibody technology in cancer, organ transplantation, and auto-immune diseases.

- Research on recombinant DNA, largely supported by the NIH, has already paid off in terms of human application. Three medical products made with recombinant DNA techniques are already being tested in clinical

trials: insulin, human growth hormone, and interferon. Dr. Bernard Moss and a team of NIH scientists have used the new technique to modify Vaccinia virus--used for 200 years to produce immunity to smallpox--so that it can confer protection against influenza and hepatitis B. Work with animals suggests that the Vaccinia virus can be used for safe, effective, and inexpensive vaccines that can be stored and administered easily. These would protect against a wide range of infectious diseases.

- o Recently, a private laboratory announced the isolation of the gene for the component of blood (Factor VIII) necessary for clotting. This discovery is expected to permit the production, through biotechnology, of artificial Factor VIII in the volume needed for the treatment of the Nation's 25,000 hemophiliacs and at much less than current cost. We also can expect early development of applications of monoclonal antibody and recombinant DNA techniques to modify the immune response in organ transplants, to treat female infertility and cardiovascular disease, and to diagnose defects in a wide variety of genetic diseases such as Huntington's disease.

Recently, Nobelist Arthur Kornberg made an arresting forecast on the near future of biomedical research by observing, "I am confident that within five years the most exciting prospects for medicine and industry will be subjects and products no one now even talks about." He went on to comment, "The currently active scientists who will lead these new advances are already bored with cloning and sequencing DNA and making hybridomas. Gifted young people entering biologic science will not join the "cloning pack" for hormones and vaccines, but will devise new techniques to solve more challenging problems."

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Against this background of accomplishment and promise, permit me to present in the broadest outline our plans and budget for the coming year.

The President's 1985 budget request for the National Institutes of Health is $4,566,453,000 in budget authority. This represents an increase of $89,118,000 over the 1984 level.

The 1985 request would support an estimated 5,000 new and competing renewal research project grants. Added to the active continuation grants, the 1985 awards will bring the total of ongoing research project grants to 17,094. The average cost per grant of both the competing and continuing categories will be increased by approximately five percent. The 1985 proposal also provides funding for the full amount of indirect costs of research grants.

In the aggregate, the other mechanisms, such as research centers, research career programs, biomedical research support, research contracts, and intramural research will be funded at levels approximating the 1984 level.

The request for 1985 calls for funding to support approximately 9,000 research trainees, a reduction of about 9 percent from the estimated 1984 level of 9,863. The budget request includes a 5 percent increase in the stipend level for trainees.

Provision is made in the budget for continuation of two of our major modernization efforts. An amount of $4,200,000 is requested for repairs and improvements of physical plants; $6,900,000 is requested for the seventh year of the program to modernize the Warren Grant Magnuson Clinical Center. The intramural laboratory renovation program is proceeding with funds appropriated in 1984 to modify the first of the six buildings in the plan.

Finally, the 1985 request anticipates the collection of $7,500,000 in fees for the cost of patient care in the Clinical Center not directly related to research. Such costs are normally reimbursable in a non-Federal health care institution. Funds collected would be used to offset intramural clinical research expenses. The Department is examining the need for further legislation to implement this policy and is proposing appropriation language to permit the NIH to receive and use such cost recoveries.

In sum, the 1985 request for NIH represents a realistic level of Federal support for biomedical research and research training. The request emphasizes support for basic research and provides a 5 percent increase in research project grant average costs. In other funding mechanisms, the request supports ongoing programs at basically the 1984 enacted levels. Overall, the 1985 budget request reflects the Administration s commitment--even in a time of constrained resources--to a vigorous program of biomedical research and training.

Mr. Chairman, I wish to express appreciation to this Committee for its key role in making it possible for NIH to acquire the 11-acre convent property at the western edge of the NIH campus, formerly owned by the Order of Visitation. The property was transferred to the NIH November 16, 1983. After modest renovations, we will shortly be able to put the convent building to interim use for certain limited research activities and for sorely needed research conference space. In the long term, this strategically located property will be of great value for the development of NIH programs.

I am grateful for the opportunity you have given me to present this overview of the FY 1985 budget for the National Institutes of Health. More specific information will be presented in subsequent testimony by the Directors of our Bureaus, Institutes and Divisions. I hope that all of this information will be useful to you in making your difficult decisions on the allocations of public resources.

I will be pleased to answer any questions you may have.

OPENING REMARKS*

by

James B. Wyngaarden, M.D.**

I am delighted to open the "NIH Workshop on Nutrition and Hypertension" which is cosponsored by the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Aging (NIA), and the NIH Nutrition Coordinating Committee (NCC), which operates out of my office.

This is an international workshop and therefore I would like to welcome particularly those scientists from Germany and Japan, as well as all other participants here today.

Each year the NIH Nutrition Coordinating Committee cosponsors with other NIH Institutes and Agencies of the Department of Health and Human Services a nutrition workshop on a subject of research interest to more than one NIH Institute or Agency. The Workshop on Nutrition and Hypertension is this year's NCC workshop. Certainly, high blood pressure is a major research interest of the NIH, as well as a very important public health issue. In previous years the NCC has sponsored workshops on such topics as "The Assessment of Nutritional Status" and "Body Weight, Health, and Longevity"; a summary of the latter was recently printed in the February 1984 issue of the Annals of Internal Medicine.

The NIH-sponsored nutrition workshops are an important mechanism used by the NIH to help expedite the transfer of nutrition information to the

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*NIH Workshop on Nutrition and Hypertension, Bethesda Marriott Hotel, March 12, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

scientists and educators so as to assure the appropriate application of research in practice. In addition, these workshops often lead to the publication of Program Announcements, Requests for Applications, and Requests for Proposals in different areas of nutrition research and thus help to expand the nutrition research program of the NIH.

As all of you are aware, nutrition research and training at the NIH are supported by the 11 Institutes and the Division of Research Resources (DRR). The total support for the NIH program in biomedical and behavioral nutrition research and research training for FY 1983 was $164,306,000, which represents an increase of 13.8 percent over the FY 1982 support of nutrition research.

Research in the various aspects of hypertension is supported primarily by NHLBI and DRR, although aspects such as the role of obesity in hypertension and the relationship of hypertension to age are supported by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), the National Institute of Child Health and Human Development (NICHD), and the National Institute on Aging (NIA).

Later this morning, Ms. Nancy Ernst, NHLBI, will report on the NIH-supported research on nutrition hypertension.

For many years, the intramural program of the NIH has carried out research on the renal aspects of hypertension, as well as the role of sodium, potassium, and magnesium in the development of hypertension. The two NHLBI intramural scientists who will be presenting papers at the workshop are Dr. J. Gill on "Laboratory Methods in Nutrition Research" and Dr. W. Lovenberg on "Dietary Protein, the Central Nervous System, and Hypertension."

As I look over the program for the workshop, I am impressed by the many topics--"-Dietary Topics"--that are mentioned, as well as the number of

clinical investigators assembled here to review and define the role of diet in hypertension.

Workshops of this nature are very important because they help us to review the scientific information and define the research needs necessary for the early identification and management of the patient with high blood pressure. I therefore encourage each of you here to be as critical as you can in your deliberations. As I look over the audience, I can see that many of you sit on the NIH Councils and Study Sections, and are NIH grantees. I am also glad to see the scientists from USDA.

I commend the Institutes and the Nutrition Coordinating Committee for their cooperative spirit and interest in expanding nutrition research at the NIH through this workshop. Again, I welcome each of you and I certainly look forward to your deliberations.

INTRODUCTORY REMARKS*

by

James B. Wyngaarden, M.D.**

In 1982 when J. Michael Bishop shared the Albert Lasker Basic Medical Research Award, his citation read: "For his fundamental and far reaching discoveries concerning the nature of oncogenes and their profound importance, and for determining that closely related genes occur not only throughout the animal kingdom, but within the genome of cancer causing retroviruses in humans."

Oncology, and indeed all biomedical science, has progressed to the molecular level. After centuries of varying and often opposing hypotheses on the cause and nature of cancer, we now have an outline of a unifying concept of abnormal growth linking viruses, chemicals, and cancer. This link is the oncogene.

The oncogene concept suggests that, in the course of evolution, a certain type of virus became incorporated in the genetic structure of the individual, existing as an inactive infection before birth. This "oncogene" can be activated later by unknown catalysts. Oncogenes have been found in animal tumor viruses. More recently, researchers, including our speaker this evening, have made the astounding discovery that similar oncogenes are found in the genetic dowry of every form of animal from fish to humans.

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* For Dr. Michael Bishop, NIH Lecturer, March 21, 1984.

** Director, National Institutes of Health, Bethesda, Maryland.

Dr. Bishop began his distinguished career studying the genetic material of viruses and how it is replicated and expressed. He then turned to the investigation of the potential relationship between certain viruses and the development of cancer, concentrating on a family of viruses called RNA tumor viruses.

Dr. Bishop and his colleagues have made discoveries that have vastly improved our understanding of the origins of human cancer. Not only have they found that oncogenes are found in all animals but that they may be, in fact, essential to normal growth and development. Oncogenes may become dangerous only when captured by a particular virus or when these activated cancer genes, unleashed from their normal controls, are expressed at very high levels.

These findings are fundamentally important to various aspects of cancer research. They may lead to a better understanding of the susceptibility of cells to cancerous transformation by environmental, hormonal, or other factors. Dr. Bishop is a leading contributor to this new paradigm.

Dr. Bishop received his M.D. from Harvard Medical School in 1962. He completed two years of training in internal medicine at Massachusetts General Hospital and was a Research Associate in the National Institute of Allergy and Infectious Diseases' Laboratory of the Biology of Viruses. Dr. Bishop is currently Director and Professor of the Department of Microbiology & Immunology at the University of California, San Francisco.

Tonight we are honored to have Dr. Bishop deliver the NIH Lecture, "Cancer Genes Come of Age."

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

When I sent word to Dr. Diwan that I would be delighted to accept her invitation to participate in this forum, I cautioned that I might be forced to cancel because of our annual budget hearings. At the time, we only knew that the hearings would be sometime in March or April. It turned out that the House Hearings began March 7, and the six days of presentations were completed last week. We are scheduled to repeat the performance before the Senate Appropriations Committee beginning a week from next Tuesday, on April 3.

One might say that just now we are in the "eye of the storm." Although it isn't entirely appropriate to equate the hearings to a hurricane, there are some similarities. Instead of boarding up the windows, however, we open them and invite meticulous scrutiny of our actions and plans. An enormous amount of staff and administrative effort is expended in preparing the reports and justifications needed by the Congressional Committees in making their difficult decisions about the allocation of resources, and the NIH budget is substantial. The President's request for Fiscal Year 1985 for the NIH is almost $4.6 billion.

At the hearings, we are given the opportunity to explain our accomplishments and objectives and to respond to questions from the committee members. It is not unusual for the NIH to answer more than fifteen hundred such queries, either at the Hearings or in the written follow-up to the presentations.

This year, in my formal opening statement at the House budget hearings, I emphasized a point that bears directly on government/university relations, the theme of this forum. I stressed to the Committee that in discussing the plans and budget proposals for the NIH, we are addressing broader concerns than just the support of a Federal Agency as such. I reminded the Committee that nearly 60 percent of all health-related research and development in America's universities and medical schools is funded through the NIH. In fact, almost $3.6 billion or four-fifths of the current NIH budget is being expended through extramural awards for the support of non-Federal investigators and of public and private institutions

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* Presented at Forum on Government/University Relations, Rensselaer Polytechnic Institute, Troy, New York, March 23, 1984.

** Director, National Institutes of Health, Bethesda, MD.

engaged in biomedical research. The scientists supported through NIH extramural programs together with the investigators in our intramural laboratories and clinics form a substantial element of the American biomedical research community, and have been responsible for the bulk of the significant scientific developments of the past few decades that have contributed greatly to the health and well-being of the American people.

In terms of basic biomedical research, the NIH role is even more prominent. We estimate that 90 percent of such fundamental research in this country is supported by NIH.

At the NIH, we often speak of our association with academia as a partnership. The multiple benefits realized from Federal support for the conduct of research at academic institutions was demonstrated conclusively during World War II. In the succeeding years, the NIH-academic partnership for biomedical research has become an outstanding example of the advantages of such collaboration.

In March 1983, the President's science advisor, George Keyworth, speaking at a AAAS colloquium on research and development policy declared that in supporting research in academic institutions ". . . we are building on strength rather than trying to invent new mechanisms." He asserted that "As a group, American research universities are the best in the world, both in terms of producing the new knowledge that stimulates technology and in terms of producing the people who drive the innovative process in society. That unique dual function," he said, "explains our tremendous emphasis on university research. No other research institutions--Federal laboratories, nonprofit organizations, or industrial laboratories--give so much return on investment in the long term. No other institutions produce both knowledge and people."[1]

Dr. Keyworth's view of the partnership was echoed in the results of an opinion survey conducted recently by Louis Harris and Associates.[2] A sample of more than 1,200 leaders and other members of the general public was asked to agree or disagree with the statement, "The Federal Government should increase by a sizable amount the money they give to colleges and universities for basic scientific and technological research."

Sixty-eight percent of the persons interviewed agreed with that statement, only 28 percent disagreed. Even a higher proportion (70 percent) of that part of the sample made up of Congressmen and their top aides agreed that the Federal contribution to academia for research should be increased by a

sizable amount. Perhaps even more significant was the perception by 64 percent of the Congressional cohort that the general public would agree with such increases. As you might expect, we have included information about this survey in our Congressional testimony.

Substantial funding continues to be crucial for the nurture of the biomedical research enterprise, but the mechanisms used for providing such support are also key elements in making the most strategic uses of available resources.

The backbone of NIH extramural activity is the investigator-initiated research project, a mechanism that makes it possible for our programs to draw upon the creativity of the entire research community. A substantial amount, just over half, of NIH-supported research is performed in medical schools, but over one-sixth of our extramural funds are awarded to other institutions of higher education. During 1983, Rensselaer Polytechnic Institute, for example, had nineteen NIH investigator-initiated research project grants for a total of about $1.7 million.

Well over half (54.5 percent) of our total budget request for 1985 is allocated to project grants for the support of the research proposed by individual investigators. However, our current budget makes it possible for the NIH to fund only a little over one-third of the proposals considered to be worthy of support.

Members of the scientific community, especially the faculty of academic institutions, are relied upon in large measure for advice as to which grant applications should be given priority for funding. The difficult selection process is carried out with the assistance of some 2,000 non-Federal scientists who serve as members of the advisory groups that make up the NIH peer review system.

We not only consider the investigator-initiated research project as the prime mechanism for carrying out our mission, we are also convinced that these project grants are effective instruments in helping to maintain the vigor and momentum of the American biomedical research enterprise. The continued availability of a reasonably predictable level of support of such grants has special meaning for individual members of the research community, especially for young investigators beginning their research careers. Trends in the levels allocated to new and competing renewal NIH grants are watched closely. For many, they represent a kind of index of research opportunity.

The 1985 budget request for NIH calls for the support of an estimated 5,000 new and competing research grants. The average NIH grant is for a period of three to four years and when our continuing commitments are added to the 5,000, the total number of research project awards predicted for 1985 will be above 17,000.

The goal of funding at least 5,000 new and competing awards each year atop the continuing commitments is one facet of an overall strategy--the so-called stabilization initiative--designed to meet the need for long-term stability in the funding of health research. One of our major goals has been to minimize year-to-year fluctuations in the number of new and competing renewal grants.

While it is true that NIH has supported at least 5,000 such grants each year since 1980--and in 1984 the total is expected to be 5,272--it would be incorrect to contend that maintenance of this number per se has produced stability for the biomedical research enterprise overall. The fact that we have found it necessary to fund research project grants at support levels below those recommended by peer reviewers is a chronic source of concern to all involved. Moreover, repeated and unpredictable reductions in the fraction of total NIH dollars available for all other funding mechanisms, including training and research career awards, research centers and contracts, has led to less than desirable levels of effort in complementary areas.

Those of you who have kept in touch with NIH over a period of years know that soon after our annual budget reached the billion dollar mark in the mid-sixties, the rate of growth began to taper off, and that for the past decade, the year-to-year increases have barely kept pace with inflation.
(Slide 1 - Total NIH Appropriations - FY 1974-1984)

As early as 1974, the NIH had begun accommodating to a relatively constant budget by shifting funds among its various support mechanisms so that it could award more project grants in response to an increasing number of excellent investigator-initiated applications. The need for such shifts has been heightened by our efforts to assure that 5,000 new and competing grants would be awarded each year.
(Slide 2 - Allocation of NIH Awards - FY 1972-1983)

Despite the untoward side effects of the recent partial implementation of a stabilization policy, the NIH has no desire to abandon the concept, and we recognize the positive effect of even an incomplete application of this long-range plan during a time of fiscal stringency. It is our conviction that the important needs addressed by the original stabilization plan remain and that the essential components of the strategy continue to be vital as means for addressing those needs.

The 1985 budget request also provides for the support of 9,000 research trainees, a reduction of about 9 percent from the estimated 1984 level of 9,863, but it includes funds for a 5 percent increase in the stipend levels.

Over the past five years, the NIH has supported an average of 10,600 trainees per year, a number that represents 98 percent of the level recommended by the National Academy of Sciences. However, the trend is downward. In 1980, the budget for training was just over 5 percent of the total NIH budget. By 1984, training's share of the budget had been reduced to 3.7 percent, and the 1985 share is slightly lower.

At the December meeting of the NIH Director's Advisory Committee, I asked the group to begin considering several key questions related to manpower development. These questions were asked in the context of our common concerns about the need to support the most promising young people with the best possible training mechanisms to carry out research missions in the years to come.

For example, the Committee was asked to consider such questions as:

- o "Should the size of our manpower development programs be tied to our guesses about future levels of public support for health research?"

- o "Is there an optimum level of investment in training?"

One of the issues for consideration is of special interest to the institutions engaged in our training programs. We asked, "What are the elements that lead to the production of successful investigators?" Our research environment is becoming technologically ever more complex. Are we encouraging new clinical investigators, for example, to seek enough research training and experience in this new environment to expect them to compete successfully in our research grant program? Should we examine the kind of training they are receiving and the characteristics of the most effective training programs?

And, finally, we asked the Advisory Committee to address the question of a proper mix of manpower development programs. We support predoctoral students, postdoctoral fellows, and trainees. Some mechanisms may be serving our purposes better than others. Some that were successful 20 years ago may be less so today.

The stipend issue remains a vexing one, particularly the question of what should be done about stipends for predoctoral trainees. On all of these matters, we have more data than resources at this time.

Any useful discussion of biomedical research policy must take into account the recent pace of discovery, especially in the realm of molecular biology. Exploitation of our rapidly expanding knowledge in this field is opening new vistas for improvements in prevention, diagnosis, and treatment of many diseases.

These recently discovered and applied techniques in molecular biology have been responsible for significant health-related developments. At the same time, they have led to the creation of totally new industries. Recently, the Congressional Office of Technology Assessment released a comprehensive analysis of commercial biotechnology. From its exhaustive studies, the OTA concluded that the United States has a commanding lead worldwide in the development and application of the new biotechnology. The study pointed out that the private sector in this country invested more than a billion dollars in 1983 to commercialize recombinant DNA, cell fusion, and other related technologies that were developed with public funds directed toward biomedical research. Most of the basic research leading to these developments was conducted by or supported through NIH. An essential factor in this spectacular advance and one on which future growth will depend is the availability of young scientists trained by the NIH.

In this connection, I should note current developments that are increasingly affecting the long-standing Federal-academic partnership. Recently, we have seen the beginnings of a three-way partnership involving industry as a participant. There have been suggestions that the NIH take some kind of active part in the institution of these new relationships. We have not done so. We believe it preferable that the new forms of joint endeavor continue to evolve as they have been with the Government playing a facilitative role. Notwithstanding the fact that the areas of collaboration between the universities and industry have broadened significantly, I believe it safe to predict that the government will continue as the principal source of funding for basic research.

George Keyworth has commented that ". . . in spite of industry's increased spending for its own research and development, we have no illusions that the private sector is going to relieve the Federal Government of its responsibilities for the support of basic research."[1] He fortified that point by adding further that "There is no question that stable funding for basic research has to be a high priority for all of us."[1]

Lewis Thomas commented on the role of basic research in business terms. He said, "We are beginning to draw from a bank of stored information in biomedical science, and I

suspect we are doing something like this in the physical sciences as well." He warned, "There is some danger that the need to continue depositing new information in that bank will be overlooked in the pressure for quick application."[3]

His argument, with which I strongly agree, is that we must continue to gamble on imaginative ideas that have a high probability of not turning out as predicted--that we must be willing to run the risks of being wrong. Otherwise, he said, "the country's basic science effort will come to a standstill, and the bank will go empty."[3]

In partnership with institutions like the Rensselaer Polytechnic Institute, it is our firm intention to assure not only the solvency but the growth of this essential national resource.

References

[1]G. A. Keyworth II, "Federal R&D and Industrial Policy," Science, June 10, 1983, pp. 1122-1125.

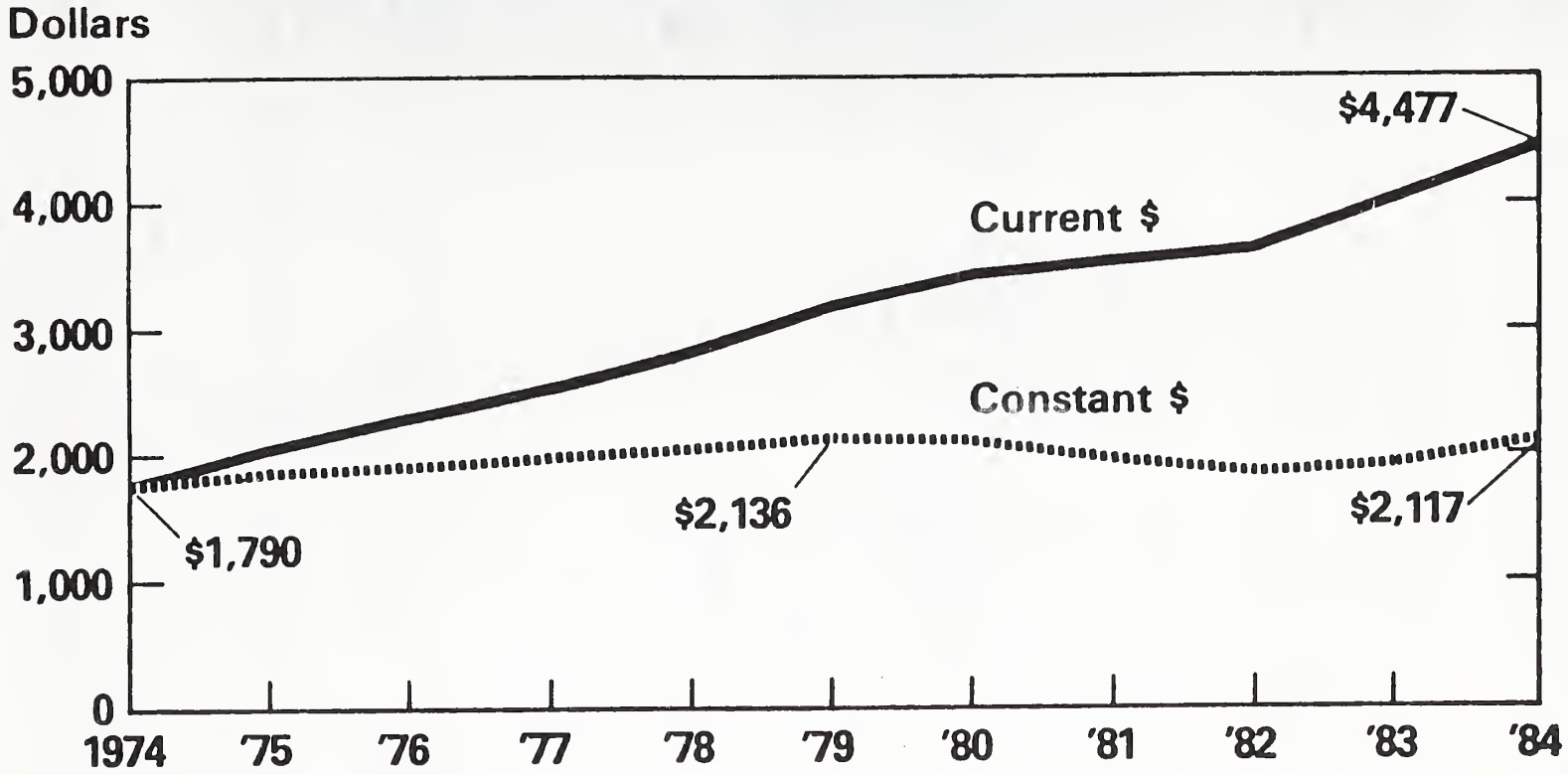
[2]"The Road After 1984 - The Impact of Technology on Society," a study by Louis Harris and Associates, December 7, 1983.

[3]"Notes of A Biology Watcher--on Science Business," New England Journal of Medicine, January 17, 1980, pp. 157-158.

(A-3)

Total NIH Appropriations, FY 1974-1984

In Current and Constant Dollars* (Millions)

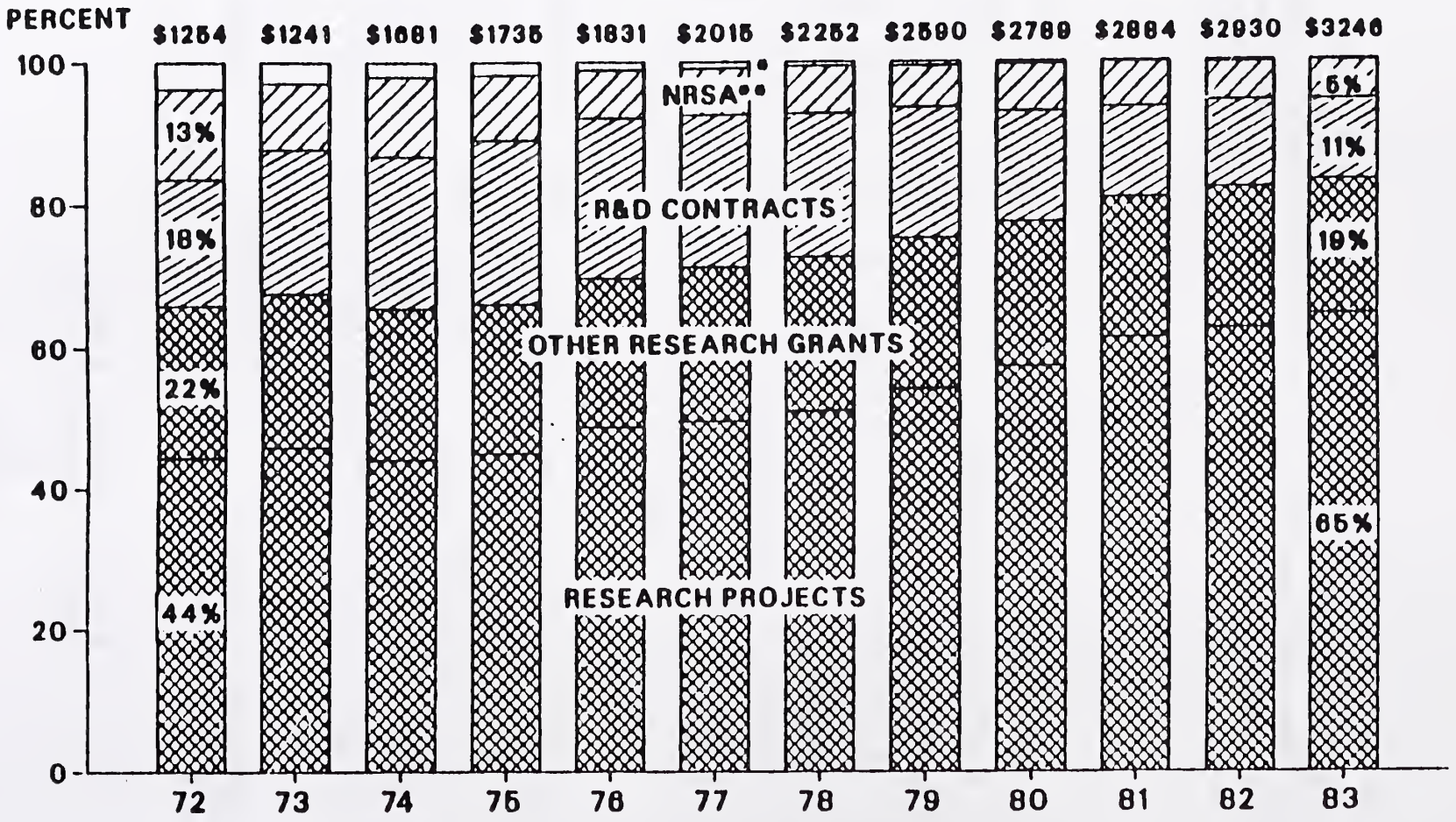


*Constant dollars are based on the Biomedical R&D Price Index, FY 1974 =100.

Source: NIH/ADA/DFM, March 13, 1984.

SLIDE 2
(C-2)

ALLOCATION OF NIH EXTRAMURAL AWARDS BY ACTIVITY, FISCAL YEARS 1972-1983
PERCENT OF AMOUNT AWARDED (CURRENT DOLLARS IN MILLIONS)



NOTE EXCLUDES TO. SEE TECHNICAL NOTE ON PAGE III FOR ACTIVITY COVERAGE
*INCLUDES CONSTRUCTION AND MEDICAL LIBRARY GRANTS **INCLUDES PRE-NRSA TRAINING.
SOURCE NIH, DRG, STATISTICS AND ANALYSIS BRANCH, 3/84.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

DR. BILLINGS -- IT IS WITH PLEASURE AND GRATITUDE THAT I ACCEPT FOR THE NIH YOUR GENEROUS GIFT.

THESE UNIQUE PAINTINGS DEMONSTRATE IN A SPECIAL WAY THE APTNESS WITH WHICH YOU HAVE COMBINED YOUR SKILLS OF OBSERVATION AS A PHYSICIAN WITH SKILLS OF EXPRESSION AS AN ARTIST. THE PAINTINGS DESCRIBE BETTER THAN THOUSANDS OF WORDS THE SUBJECTIVE EFFECTS OF MACULAR DEGENERATION.

THE PICTURES WILL SERVE TO REMIND THE NIH COMMUNITY THAT THE INDIVIDUAL PATIENT IS AT THE CENTER OF ALL OUR EFFORTS. THE ABSTRACTIONS OF MOLECULAR BIOLOGY, THE NEUROSCIENCES AND EPIDEMIOLOGY ARE FASCINATING AND POWERFUL TOOLS--BUT THEY ARE ONLY MEANS FOR ASSURING THAT IN THE FUTURE INDIVIDUALS WILL NOT FACE THE DEVASTATING HANDICAPS SO WELL EXPRESSED BY THESE PICTURES. WE ALL LOOK FORWARD TO THE DAY WHEN THESE PAINTED STUDIES WILL BE CURIOSITIES--RELICS OF THE PAST.

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*Presentation of Paintings by Dr. Terrence Billings, ACRF Lobby, National Institutes of Health, March 26, 1984.

**Director, National Institutes of Health, Bethesda, MD.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

DR. BILLINGS -- IT IS WITH PLEASURE AND GRATITUDE THAT I ACCEPT FOR THE NIH YOUR GENEROUS GIFT.

THESE UNIQUE PAINTINGS DEMONSTRATE IN A SPECIAL WAY THE APTNESS WITH WHICH YOU HAVE COMBINED YOUR SKILLS OF OBSERVATION AS A PHYSICIAN WITH SKILLS OF EXPRESSION AS AN ARTIST. THE PAINTINGS DESCRIBE BETTER THAN THOUSANDS OF WORDS THE SUBJECTIVE EFFECTS OF MACULAR DEGENERATION.

THE PICTURES WILL SERVE TO REMIND THE NIH COMMUNITY THAT THE INDIVIDUAL PATIENT IS AT THE CENTER OF ALL OUR EFFORTS. THE ABSTRACTIONS OF MOLECULAR BIOLOGY, THE NEUROSCIENCES AND EPIDEMIOLOGY ARE FASCINATING AND POWERFUL TOOLS--BUT THEY ARE ONLY MEANS FOR ASSURING THAT IN THE FUTURE INDIVIDUALS WILL NOT FACE THE DEVASTATING HANDICAPS SO WELL EXPRESSED BY THESE PICTURES. WE ALL LOOK FORWARD TO THE DAY WHEN THESE PAINTED STUDIES WILL BE CURIOSITIES--RELICS OF THE PAST.

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*Presentation of Paintings by Dr. Terrence Billings, ACRF Lobby, National Institutes of Health, March 26, 1984.

**Director, National Institutes of Health, Bethesda, MD.

CREATIVITY IN BIOMEDICAL RESEARCH*

by

James B. Wyngaarden, M.D.**

I appreciate very much your gracious invitation to deliver this 28th Annual Landacre Lecture, especially since this year it is marking the sesquicentennial of the faculty of medicine of Ohio State University. This year's Landacre Day--in addition to stimulating the continued pursuit of medical and general scientific research--also marks the role that research has played in the history of academic medicine. In appearing here today, I am doing something that I have looked forward to with keen anticipation. It is always a pleasure to listen to students deliver what are probably their very first research papers. I hope that for many of you, there will be more.

My pleasure in being here today is accompanied by a warm glow of nostalgia. Prior to coming to my present position about two years ago, my entire professional career had been devoted to academic medicine and biomedical research, with a heavy emphasis upon research training at student and house staff levels. I am mindful of the special honor and privilege your invitation represents, for this is indeed a unique assembly. Special tribute is due the men who originated the idea of the Landacre Student Honor Society back in 1956, to the faculty members who recognized the merit of their plans, and particularly to the students, past and present, who have put forth the extra effort required to undertake research projects when demands on time and intellectual energies are so great.

I hope that this taste of the excitement of research will stimulate at least some of you to enter research careers. Since becoming Director of the National Institutes of Health, I have become even more strongly convinced than before of the vital importance of attracting the ablest and brightest to careers in research, especially the need to interest and hold young men and women who are trained as physicians. Fortunately, the supply of Ph.D. scientists has held up well, but the production of physician-scientists is widely viewed as below desirable levels. In my statements to top officials in the Administration, to the Congress, and to the public, the need has been a recurrent theme, and I plan to continue that emphasis.

Back in Washington, my colleagues and I are in the midst of our annual budget hearings--for Fiscal Year 1985--before the House and Senate Appropriations Committees. At the top of our minds throughout the process of developing the budget we are now defending, was the awareness of our need to recruit and retain the ablest and best young physicians in research careers.

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*The 28th Annual Landacre Lecture, Ohio State University College of Medicine, Columbus, Ohio, March 29, 1984.

**Director, National Institutes of Health, Bethesda, Md.

While it is true that a career in research could represent a sacrifice, I think this group, more than most, would appreciate the wisdom of a statement made by Dean John Bernard Henry of Georgetown University School of Medicine when he spoke to an entering freshman class.[1] Let me repeat a portion of it.

He said, "The laboratory seldom seems to beckon with the same drama and excitement as the hospital, but let me assure you it is there. The laboratory and the classroom are the parents of medicine. It could not have been born without them.

"All that this profession is and has become is based on investigation and research. Someone, somewhere, sometime had an inquiring mind and the intelligence and stick-to-itiveness to labor long hours with one goal in mind: discovery. And it is their discoveries and their accomplishments that enable us to treat our patients and exercise our profession. We would have no knowledge to impart had someone not investigated."

A second major element of my budget testimony concerns the momentum of science. Never before has excitement seemed so intense or the promise so great for spectacular achievements against major diseases that afflict mankind. A well-conceived emphasis on maintaining a productive community of basic scientists has paid off in terms of the store of fundamental knowledge now at hand. The knowledge accrued in just the last ten years in virology, molecular biology, pharmacology, cell biology, and immunology opens up infinite opportunities for applications to clinical problems. Continued research on hybridomas, recombinant DNA technology, and oncogenes, for example, will soon need for further advancement the input of more clinical investigators.

My topic today, however, relates directly to the process of discovery itself. The title of this address is "Creativity in Biomedical Research."

Creativity is not easy to define. The dictionary lists such synonyms as originality, inventiveness, productivity, ingenuity, and novelty. These terms imply new insights, new associations, relationships and interpretations. They imply discovery plus integration into a larger body of knowledge, the evolution of new perceptions, perhaps of new paradigms. For those who are not acquainted with the book, I recommend Thomas Kuhn's The Structure of Scientific Revolutions, in which he develops the theme that science grows not by continuous, smooth expansion, but rather by the development of new paradigms, new insights that give rise to new operational tenets that give new directions to emerging fields.[2]

One of the greatest discoveries in biological science of all time--a suggested structure for DNA--was published about 30 years ago by Watson and Crick. Their then new paradigm may quite plausibly be credited with inaugurating the biological revolution. This revolution has led to the confluence of previously separate scientific disciplines, and as a result such segmented fields as anatomy, physiology, pharmacology, microbiology, biochemistry, and pathology now share a common scientific base reflected in the relatedness of virtually all current scientific inquiry: the genetic control of structure, development, and function.

But let me take you back a bit to the pre-Watson-Crick days. While on the one hand I envy you your vast scientific opportunities and the array of concepts and methods awaiting your exploitation, on the other I am happy to have entered the scene when I did, to have been able to see the revolution unfold, and to have played a small part in it.

When I was a medical student, DNA was thought to contain four bases--adenine, guanine, cytosine, and thymine--and to be comprised of a regularly recurring tetranucleotide structure-- purine, pyrimidine; purine, pyrimidine. This putative structure for DNA had been taught as dogma for 50 years, since the days of P. A. Levine who proposed this structure in about 1900. Virtually every textbook of biochemistry of the first half of the twentieth century taught that structure.

In the early 1940s, DNA was established as genetic material, and questions were soon raised as to how DNA of such regular structure could contain genetic information. The development of chromatographic methods made it possible to analyze base ratios of purified, hydrolized DNA. This work was done principally by Erwin Chargaff of Columbia, who found that the ratios of the four purine and pyrimidine bases were not always one to one to one to one. From extensive analyses of DNA from many species, he described certain regular relationships, later called by others "Chargaff Rules." These are as follows: (a) the sum of the purines (adenine and guanine) equals that of the pyrimidines (cytosine and thymine); (b) the molar ratio of adenine to thymine equals 1; (c) the molar ratio of guanine to cytosine equals 1. And, as a direct consequence of these relationships, (d) the number of 6-amino groups (adenine and cytosine) is the same as that of 6-keto groups (guanine and thymine).

Chargaff had discovered some extraordinary principles of complementarity, but there he stopped. He did not attempt to speculate from his data on the primary, secondary, or tertiary structure of DNA. Meanwhile, others were addressing these problems. Pauling and Corey proposed a triple-stranded model of DNA, based on x-ray diffraction diagrams that they misinterpreted. Watson and Crick were building models of DNA and were aware of Chargaff's findings. They eventually came to a two-stranded double helical model of DNA, which incorporated the Chargaff rules of complementarity, and fit the x-ray diffraction diagrams of Pauling, as later shown by Rosalyn Franklin. In their original publication in Nature some 30 years ago, they offered a suggested structure of DNA, and a hypothesis as to how this structure would encode information, form a basis for replication, for mutation, and heredity.

I find the contrasting contributions of Chargaff and of Watson and Crick enormously instructive. Chargaff's contribution was careful, analytical, precise, and cautious; Watson and Crick's imaginative, synthetic, speculative, and insightful.

In his autobiography, "Heraclitean Fire,"[3] Chargaff describes himself as "imaginative rather than analytical." I would have described him just the other way, showing the difficulty in seeing ourselves as others see us.

Creativity takes many forms. It carries with it the spirit of inquiry and the application of curiosity and imagination leading to discovery. Imagination is a kind of latent creativity. It is natural for young people to be imaginative, and if this imagination can be coupled with discipline, its energy can be a life-long strength. The philosopher Alfred North Whitehead called it a tragedy that "those who are imaginative have but slight experience, and those who are experienced have feeble imagination." He then generalized to say that "fools act on imagination without knowledge: pedants act on knowledge without imagination."[4] The trick is to retain imagination while gaining a fund of experience and knowledge.

It is not easy to describe the process of creativity. Sir William Osler[5] had his simple explanation for creativity that led to progress in medicine. He said, "A master word is directly responsible for all advances in medicine over the past 25 centuries. The master word is 'work'."

But in Sir Alexander Fleming's account of the discovery of penicillin, a drastically different quality of creativity is suggested; namely, the added ingredient of chance. He said, "There are thousands of different molds and there are thousands of different bacteria and that chance put that mold in the right spot at the right time is like winning the Irish Sweepstakes."[6]

The great French scientist, Claude Bernard, echoed Fleming's comment about the accidental nature of creativity but added a most important dimension to the thought. Bernard said that "experimental ideas are very often born by chance as a result of fortuitous observations. Nothing is more common and it is really the simplest way to begin a piece of scientific work. We walk, so to speak, in the realm of science, and we pursue what happens to present itself accidentally to our eyes."[7]

The same thought was economically expressed by Franklin P. Adams when he said, "I find that a great part of the information I had was acquired by looking up something and finding something else on the way."[8] Perhaps it is useful to emphasize the fact that the Adams' process was begun by looking up something. Serendipity is a dividend of activity. The word serendipity has an interesting history. It was invented by Horace Walpole in a letter he wrote to a friend about a fairy tale, "The Three Princes of Serendip." Serendip was an ancient name for Ceylon or Sri Lanka. He wrote, "As their highnesses traveled they were always making discoveries, by accident or sagacity, of things which they were not in quest of." Serendipity has come to mean the discovery of one thing when in search of another.

In his recent book, "The Youngest Science," Lewis Thomas placed these insights of Claude Bernard and Franklin P. Adams squarely in the context of the physician researcher. He was discussing medical education and biomedical research of the 1950s and said, "The M.D. program was not then and still is not very satisfactory training for research in biomedical science. Then, as now, the Ph.D. program provided a much more rigorous and profound experience in science with a better grounding in the basic fields of biology needed for medical research. Earning an M.D. has, however, one enormous advantage that makes up in part for its deficiencies. After four years of medical school,

it is impossible to think about a problem in biology or to read a paper without having part of one's mind trying at the same time to make connections with human disease."[9]

I can't resist quoting further from Dr. Thomas' book. In one of the paragraphs he expresses in his own colorful way what he considers to be a central truth about research. He said, "Making guesses at what might lie ahead when the new facts have arrived is the workaday business of science. But it is never the precise sure-footed enterprise that it sometimes claims credit for being. It has the sound of an intellectually flawless acrobatic act. The mind stands still for a moment, leaps out into mid air at precisely the millisecond when a trapeze from the other side is hanging at the extremity of its arc, zips down, out, and up again, lets go and flies into a triple somersault; then catches a second trapeze, timed for that moment, and floats to a platform amid deafening applause. There is no margin for error. Success depends not so much on the eye or the grasp, certainly not on the imagination; only on the predictable certainty of the release of the bars to be caught--clockwork.

"It doesn't actually work out this way, and if scientists thought it did, nothing would get done. There would only be a mound of bone-shattered scholars being carried off on stretchers.

"In real life, research is dependent on the human capacity for making predictions that are wrong, and on the even more human gift for bouncing back to try again. This is the way the work goes. The predictions, especially the really important ones that turn out from time to time to be correct, are pure guesses. Error is the mode."

A few years ago, while participating in the centennial observances of the University of Colorado Health Sciences Center, I met Dr. James H. Austin, Professor and Head of the Department of Neurology there. Dr. Austin has written extensively on creativity, and he gave me a copy of his book on the subject titled "Chase, Chance and Creativity--The Lucky Art of Novelty."

In Austin's examination of serendipity, he identifies four distinct forms of chance--accidental good luck, energetic motor activities in the right territory, a special kind of receptivity and discernment unique to the recipient, and a probing action with a distinctive personal flavor which courts Dame Fortune.

His book is filled with accounts of his personal experiences as a clinician and a scientist, and he draws from these experiences a demonstration of the role of creativity in teaching, research, and practice.

Any discussion of chance and creativity in science is incomplete without the moderating words of Louis Pasteur, "Chance favors only the prepared mind."[10]

Throughout these characterizations of creativity, there are the contradictory concepts that would spell disaster for a marksman. They seem to be saying that you should aim carefully but not expect to hit the target in your sights. It brings to mind the advice given to night flyers during World War II who were told that dimly lit objects could only be seen if you did not look directly at them.

Creation in science is usually approached indirectly. There are often long periods when the person who is about to make an original observation appears to do nothing but take in information, work rather fruitlessly at seemingly trivial aspects of the problem, or give attention to unrelated matters. This is sometimes described as a period of "incubation." Following such a phase, the solution of a difficult problem or the occurrence of an original idea will often come all of a sudden in a leap of insight. It usually results from a dramatic change in the way the problem is perceived. Such a transformation can change a complicated problem into a simple one, and this sequence can be as descriptive of a difficult diagnosis as of a stubborn research problem.

It has been said that the two great enemies of creativity are mental rigidity on the one hand and wishful thinking on the other. These are evident when a person acts either in a far more regular way than the situation demands or else is incapable of perceiving the external realities that make his ideas infeasible. I would add a third enemy, namely, imitation.

These barriers to creativity are of the most difficult kind because they are self-imposed. We tend to give undue importance to established patterns of thought and lock ourselves into conformity with them. We fear to challenge the obvious lest we appear naive. For some, this fear may be an insurmountable barrier. Jacques Barzun once remarked that one cannot learn to ice skate or speak French without looking foolish, and that's why these skills are easy to the young who do not worry so much about appearances.

If you will permit one more personal digression, I would like to describe for you two contrasting behavioral patterns of two enormously creative scientists, Francois Jacob and Jacques Monod, of the Pasteur Institute in Paris, who shared the Nobel Prize for their discovery of messenger RNA. I was privileged to spend a year in that environment in 1963-64, and to participate in their Monday evening seminars for about ten months. Monod at that time was trying to understand enzyme regulation at the molecular level. There were two major theories. One, called the induced-fit hypothesis, championed especially by Daniel Koshland in which he envisioned a gradual and progressive accommodation of the macromolecule to its substrate or inhibitor as a result of contact between the protein and the ligand. The Paris school proposed the allosteric model, in which an enzyme might exist in two states, which Monod called the R&T states, for relaxed and taut configurations. He suggested that the substrate might bind with one form, an inhibitor with another, and that binding essentially removed the complex from an equilibrium state, thus progressively shifting the mixture toward either the R or the T state. Monod presented model after model of his allosteric ideas on successive Monday evenings, replete with diagrams and equations on the board. He was inviting the most searching and

critical comment from the audience which consisted of many accomplished physical biochemists, and some of the criticisms were severe indeed. The colloquia were animated, vigorous, searching and sometimes devastating, but totally devoid of any acrimony or ceremony. The youngest person in the group was free to destroy the teacher's model and Monod, always flamboyant, and highly articulate, enjoyed the sessions as his ideas were honed and improved. By contrast Francois Jacob, equally brilliant, equally creative, was quiet, attentive, introspective. Perhaps in one seminar in four, that is, once a month, he would ask a short question for verification. These two great scientists, perfectly mated, worked together with extraordinary productivity for 30 years with personalities that could not have been more different, yet in my view they were equally creative.

In an article in the Scientific American which appeared nearly 30 years ago, Morris Kline said, "The creative act owes little to logic or reason. In their accounts of the circumstances under which big ideas occurred to them, mathematicians have often mentioned that the inspiration had no relation to the work they happened to be doing. Sometimes it came while they were traveling, shaving, or thinking about other matters. The creative process cannot be summoned at will or even cajoled by sacrificial offering. Indeed it seems to occur most readily when the mind is relaxed and the imagination roaming freely."[11]

Sudden hunches, hunches that lead to short, elegant solutions of problems, are called by psychologists "Aha! Reactions"--they seem suddenly to come out of the blue.

In his delightful little book called "Aha! Insight," Martin Gardner examines the question, "Exactly what goes on in a creative person's mind when he or she has a valuable hunch?" The truth is that nobody knows. It is some kind of mysterious process that no one has so far been able to teach or to store in a computer . . . the sudden hunch, the creative leap of the mind that sees in a flash how to solve a problem in a simple way, is something quite different from general intelligence. Recent studies show that persons who possess a high Aha! ability are all intelligent to a moderate level but beyond that level, there seems to be no correlation between high intelligence and this kind of thinking. Einstein, for instance, was not particularly skillful in traditional mathematics and his records in school and college were mediocre. Yet the insights that produced his general theory of relativity were so profound that they completely revolutionized physics."[12] Martin Gardner added one other idea which I think is worth considering. He said that psychologists are not sure, but studies of creative thinking suggest some sort of relationship between creative ability and humor, which has been defined as the sensation of sudden, unexpected pleasure. Perhaps there is a connection between hunches and delight in play.

It has been known for some time that brainstorming is an efficient technique for tapping the creative idea of a group. It works best when the members of the group can suspend judgment, saving critical evaluation of ideas for later; when ideas are presented without inhibition, whether they are good or bad, sensible or silly; when there is a substantial number of ideas presented; and when there is cross-fertilization, examination of each of the ideas from the different perspectives of the individuals in the group.

According to Herodotus, the ancient Persians at the time of Cyrus the Great made a general practice of deliberating upon affairs of weight when they were drunk, and then on the next day to consider the matter again when they were sober. If they still approved of their drunken decision, they then acted upon it. Herodotus added, "Sometimes, however, they are sober at the first deliberation, but in this case, they always reconsider the matter under the influence of wine."[13] I would interpret the laughter from the audience to indicate that you agree that this is, indeed, a means for removing barriers to creativity.

Brainstorming pertains to group consideration. It has valid counterparts, however, in the process by which an individual generates creative questions and answers.

Equating creativity to chance, to leaps of insight, to suspended judgment, to acceptance of ideas without evaluation is to trivialize the accomplishments of the men and women who have brought us to this exciting day in science. Once again, let me remind you of Pasteur's admonition that chance favors only the prepared mind.

Furthermore, I cannot overlook an obvious fact about this assembly. Most of you are medical students, training for a career in service to the suffering. Your service can take a variety of forms. In recent years, we have seen the powerful benefits of increased knowledge.

In an essay on the science and technology of medicine, Lewis Thomas addressed the question of medical care in global terms. "If," he said, "our society wishes to be rid of the diseases, fatal and nonfatal, that plague us the most, there is really little prospect of doing so by mounting a still larger health care system at still greater cost for delivering essentially today's kind of technology on a larger scale. We will not do so by carrying out broader programs of surveillance and screening. The truth is that we do not yet know enough."

Thomas went on to say, "But there is also another truth of great importance: We are learning fast. The harvest of new information from the biological revolution of the past quarter century is just now coming in, and we can probably begin now to figure out the mechanisms of major diseases which were blank mysteries a few years back as accurately and profitably as was done for the infectious diseases earlier in this century. This can be said with considerable confidence and without risk of overpromising or raising false hopes provided we do not set time schedules or offer dates of delivery. Sooner or later it will go this way, since clearly it <u>can</u> go this way. It is simply a question at this stage of events of how much we wish to invest for the health care system of the future in science."[14]

Such public investment in science comes down to a highly personal and individual activity. As Alan Gregg has said, "Medical research is an abstraction. The realities are not the laboratories and the hospitals but the men and women who search again and again for causes."[15]

More than a hundred years ago, Oliver Wendell Holmes commented to a graduating class that "Science is a great traveler and wears out shoes pretty fast, as might be expected."

Since that day, the pace of science and consequently of the practice of medicine has accelerated to a fantastic rate. Perhaps it is significant to note that many statues of the Roman god Mercury had him not only carrying a caduceus but also wearing winged sandals. It may be revisionist mythology, but it seems to me that a modern medical scientist might fairly be represented by the figure of Mercury carrying the aesculapian staff of healing, and wearing winged sandals to depict the creative leaps of original discovery.

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(S.Whaley:ww)

CURRENT BUDGETARY AND ORGANIZATIONAL ISSUES AFFECTING THE NIH*

BY

JAMES B. WYNGAARDEN, M.D.**

AT THIS TIME OF THE YEAR, IT IS NOT WISE TO INITIATE A CONVERSATION WITH A FEDERAL ADMINISTRATOR UNLESS YOU ARE INTERESTED IN HEARING ABOUT BUDGET OUTLAYS, APPROPRIATIONS AND PROGRAM PLANS FOR THE COMING FISCAL YEAR. THIS IS THE SEASON FOR OUR ANNUAL BUDGET HEARINGS, A PERIOD WHEN WE MARCH UP CAPITOL HILL ARMED WITH ENORMOUS AMOUNTS OF DATA AND SUBMIT TO ORAL EXAMINATION ON WHAT WE HAVE DONE AND WHAT WE PLAN TO DO. CONSEQUENTLY, THOSE OF US WHO APPEAR AS WITNESSES MUST BE PREPARED TO EXPOUND ON A VERY WIDE RANGE OF SUBJECTS AT THE DROP OF A GAVEL.

~~OUR BUDGET OFFICE HAS TOLD ME THAT~~ IN THE COURSE OF THE HEARINGS AND IN RESPONSE TO WRITTEN INTERROGATORIES FOLLOWING THE HEARINGS, WE ANSWER MORE THAN 1,500 QUESTIONS EACH YEAR.

THE NIH HEARINGS BEFORE THE HOUSE APPROPRIATIONS SUBCOMMITTEE BEGAN MARCH 7 AND LASTED SIX DAYS. WE ARE SCHEDULED TO MAKE OUR PRESENTATIONS TO THE COUNTERPART SENATE COMMITTEE NEXT TUESDAY AND WEDNESDAY.

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*ADDRESS TO FACULTY, MEDICAL COLLEGE OF WISCONSIN, WOOD, WISCONSIN, MARCH 30, 1984.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.

I WILL RESIST GETTING CARRIED AWAY AND GIVING YOU THE FULL TREATMENT ON THE BUDGET, ~~ON THE OTHER HAND~~ EVEN THOUGH, MUCH OF WHAT WE ARE DISCUSSING WITH THE CONGRESS IS OF DIRECT CONCERN TO INSTITUTIONS LIKE THE MEDICAL COLLEGE OF WISCONSIN. ~~BUT~~ I WILL GIVE YOU A GLIMSE OF THE SITUATION.

THE PRESIDENT'S 1985 BUDGET REQUEST FOR ALL OF THE ACTIVITIES OF THE NATIONAL INSTITUTES OF HEALTH AMOUNTS TO ALMOST $4.6 BILLION. OF THIS TOTAL, OVER 80 PERCENT OR ABOUT 3.65 BILLION IS ALLOCATED TO THE SUPPORT OF RESEARCH AND TRAINING AT ALMOST 1,300 MEDICAL SCHOOLS, UNIVERSITIES, HOSPITALS, AND RESEARCH INSTITUTIONS THROUGHOUT THE NATION. THIS MEANS THAT THE FATE OF OUR BUDGET IS OF ~~CONSIDERABLE~~ GREAT CONCERN TO THE WHOLE OF THE SCIENTIFIC COMMUNITY, PARTICULARLY TO INSTITUTIONS LIKE THIS ONE THAT HAVE STRONG COMMITMENTS TO BIOMEDICAL RESEARCH. LAST YEAR, THE MEDICAL COLLEGE OF WISCONSIN WAS AWARDED MORE THAN $10 MILLION IN GRANTS AND CONTRACTS.

I HAVE POINTED OUT IN OUR APPROPRIATIONS HEARINGS THAT THE IMPLICATIONS OF THE BUDGETS WE WERE DISCUSSING ARE MUCH BROADER THAN JUST THE ANNUAL OPERATING EXPENSES OF A GOVERNMENT AGENCY--THAT WE WERE SPEAKING ON BEHALF OF A SUBSTANTIAL PORTION OF THE NATION'S ~~ENTIRE~~ BIOMEDICAL RESEARCH ENTERPRISE. NIH PROGRAMS ARE THE SOURCE OF ABOUT 37 PERCENT OF THE OVERALL TOTAL OF AMERICAN PUBLIC AND PRIVATE FUNDS INVESTED IN HEALTH-RELATED RESEARCH AND DEVELOPMENT, INCLUDING INDUSTRIES' EXPENDITURES. OUR SHARE IN FUNDING BASIC BIOMEDICAL RESEARCH IS MUCH HIGHER, ~~IT HAS BEEN ESTIMATED~~

AMOUNTING TO AN ESTIMATED ~~THAT NIH IS THE SOURCE OF~~ 90 PERCENT OF THE FUNDS USED FOR SUCH FUNDAMENTAL INVESTIGATIONS IN THIS COUNTRY.

IT WOULD BE DIFFICULT TO OVERSTATE THE IMPORTANCE WE ATTACH TO OUR PARTNERSHIP WITH ACADEMIA, A MUTUALLY BENEFICIAL RELATIONSHIP TESTED AND STRENGTHENED BY 40 YEARS OF SUCCESSFUL EXPERIENCE. THE MULTIPLE ADVANTAGES TO BE REALIZED FROM FEDERAL SUPPORT FOR THE CONDUCT OF RESEARCH AT ACADEMIC INSTITUTIONS WAS DEMONSTRATED CONCLUSIVELY UNDER THE PRESSURES OF WORLD WAR II. IN THE SUCCEEDING YEARS, THE NIH-ACADEMIC PARTNERSHIP FOR BIOMEDICAL RESEARCH HAS BEEN EXTREMELY PRODUCTIVE.

THE PRESIDENT'S SCIENCE ADVISOR, GEORGE KEYWORTH, HAS CHARACTERIZED THE GOVERNMENT'S CONTINUING POLICY OF SUPPORTING RESEARCH IN ACADEMIC INSTITUTIONS BY NOTING THAT IN DOING SO ". . . WE ARE BUILDING ON STRENGTH RATHER THAN TRYING TO INVENT NEW MECHANISMS." HE ASSERTED THAT "AS A GROUP, AMERICAN RESEARCH UNIVERSITIES ARE THE BEST IN THE WORLD, BOTH IN TERMS OF PRODUCING THE NEW KNOWLEDGE THAT STIMULATES TECHNOLOGY AND IN TERMS OF PRODUCING THE PEOPLE WHO DRIVE THE INNOVATIVE PROCESS IN SOCIETY. "THAT UNIQUE DUAL FUNCTION," HE SAID, "EXPLAINS OUR TREMENDOUS EMPHASIS ON UNIVERSITY RESEARCH. NO OTHER RESEARCH INSTITUTIONS--FEDERAL LABORATORIES, NON-PROFIT ORGANIZATIONS, OR INDUSTRIAL LABORATORIES--GIVES SO MUCH RETURN ON INVESTMENT IN THE LONG TERM. NO OTHER INSTITUTIONS PRODUCE BOTH KNOWLEDGE AND PEOPLE."[1]

DR. KEYWORTH'S HIGH PRAISE OF THE PARTNERSHIP WAS ECHOED IN THE RESULTS OF AN OPINION SURVEY CONDUCTED RECENTLY BY LOUIS HARRIS AND ASSOCIATES. A SAMPLE OF MORE THAN 1,200 LEADERS AND OTHER MEMBERS OF THE GENERAL PUBLIC WAS ASKED TO AGREE OR DISAGREE WITH THE STATEMENT, "THE FEDERAL GOVERNMENT SHOULD INCREASE BY A SIZABLE AMOUNT THE MONEY THEY GIVE TO COLLEGES AND UNIVERSITIES FOR BASIC SCIENTIFIC AND TECHNOLOGICAL RESEARCH."[2]

SIXTY-EIGHT PERCENT OF THE PERSONS INTERVIEWED AGREED WITH THAT STATEMENT, AND ONLY 28 PERCENT DISAGREED. EVEN A HIGHER PROPORTION (70 PERCENT) OF THAT PART OF THE SAMPLE MADE UP OF CONGRESSMEN AND THEIR TOP AIDES AGREED THAT THE FEDERAL CONTRIBUTION TO ACADEMIA FOR RESEARCH SHOULD BE INCREASED BY A SIZABLE AMOUNT. PERHAPS EVEN MORE SIGNIFICANT WAS THE PERCEPTION BY 64 PERCENT OF THE CONGRESSIONAL COHORT THAT THE GENERAL PUBLIC WOULD AGREE WITH SUCH INCREASES. AS YOU MIGHT EXPECT, WE HAVE INCLUDED INFORMATION ABOUT THIS SURVEY IN OUR CONGRESSIONAL TESTIMONY.

THE CHRONOLOGY OF APPROPRIATIONS FOR THE NIH SINCE THE MID-FORTIES IS AN INDEX OF THE PUBLIC'S REGARD AS REFLECTED IN THE ACTIONS OF SUCCESSIVE ADMINISTRATIONS AND CONGRESSES. THE MILLION-DOLLAR MARK WAS FIRST REACHED IN 1943. IN 10 YEARS, THERE WAS BETTER THAN A FIFTY-FOLD INCREASE. IN THE NEXT

DECADE, THE GROWTH WAS BY A FACTOR OF TWENTY, SO BY 1963 THE TOTAL APPROPRIATION WAS NEAR, IF NOT, BILLION DOLLARS. THE TWO BILLION MARK WAS REACHED IN 1972, THREE BILLION BY 1979, AND FOUR BILLION BY 1983.[3]

THE PARTNERSHIP CONCEPT--HEAVY RELIANCE UPON THE NATION'S ACADEMIC INSTITUTIONS IN CARRYING OUT THE NIH MISSION--HAS BEEN MAINTAINED WITHOUT CHANGE FOR ALMOST 40 YEARS.

AS IMPORTANT AS SUBSTANTIAL FUNDING HAS BEEN AND CONTINUES TO BE FOR THE NURTURE OF THE BIOMEDICAL RESEARCH ENTERPRISE, THE MECHANISMS USED FOR PROVIDING SUCH SUPPORT HAVE PROVED TO BE THE KEY ELEMENTS IN MAKING THE MOST STRATEGIC USES OF AVAILABLE RESOURCES. THE BACKBONE OF NIH EXTRAMURAL PROGRAMS IS THE INVESTIGATOR-INITIATED RESEARCH PROJECT. WELL OVER HALF (54.5 PERCENT) OF OUR TOTAL BUDGET AS REQUESTED FOR 1985 IS ALLOCATED TO PROJECT GRANTS FOR THE SUPPORT OF THE RESEARCH PROPOSED BY INDIVIDUAL INVESTIGATORS. IN THIS WAY, THE NIH DRAWS UPON THE CREATIVITY OF THE ENTIRE AMERICAN SCIENTIFIC COMMUNITY.

EXPERIENCE OVER THE YEARS HAS CONVINCED US THAT INVESTIGATOR-INITIATED PROJECT GRANTS ARE ALSO EFFECTIVE INSTRUMENTS IN HELPING TO MAINTAIN THE VIGOR AND MOMENTUM OF THE AMERICAN BIOMEDICAL RESEARCH ENTERPRISE. THE CONTINUED AVAILABILITY OF A REASONABLY PREDICTABLE LEVEL OF SUPPORT FOR SUCH GRANTS HAS SPECIAL MEANING FOR INDIVIDUAL MEMBERS OF THE

RESEARCH COMMUNITY, ESPECIALLY FOR YOUNG INVESTIGATORS BEGINNING THEIR RESEARCH CAREERS. TRENDS IN THE LEVELS ALLOCATED TO NEW AND COMPETING RENEWAL NIH GRANTS ARE WATCHED CLOSELY. FOR MANY, THEY REPRESENT A KIND OF INDEX OF RESEARCH OPPORTUNITY.

THE 1985 BUDGET REQUEST FOR NIH CALLS FOR THE SUPPORT OF AN ESTIMATED 5,000 NEW AND COMPETING RESEARCH GRANTS. THE AVERAGE NIH GRANT IS FOR A PERIOD OF THREE TO FOUR YEARS, AND WHEN OUR CONTINUING COMMITMENTS ARE ADDED TO THE 5,000, THE TOTAL NUMBER OF ACTIVE RESEARCH PROJECTS PREDICTED FOR 1985 WILL BE ABOVE 17,000. THE AGGREGATE AVERAGE COST PER GRANT FOR BOTH THE NEW AND CONTINUATION AWARDS WILL BE APPROXIMATELY FIVE PERCENT HIGHER THAN IN 1984. FULL INDIRECT COSTS WILL BE PAID ON NIH GRANTS IN BOTH 1984 AND 1985. THE PROPOSED BUDGET WILL PERMIT US TO AWARD AN ESTIMATED 30 PERCENT OF THE MERITORIOUS PROPOSALS WE ANTICIPATE DURING 1985.

THE GOAL OF FUNDING AT LEAST 5,000 NEW AND COMPETING AWARDS EACH YEAR ATOP THE CONTINUING COMMITMENTS IS ONE FACET OF AN OVERALL STRATEGY--THE SO-CALLED STABILIZATION INITIATIVE--DESIGNED TO MEET THE NEED FOR LONG-TERM STABILITY IN THE FUNDING OF HEALTH RESEARCH. ONE OF OUR MAJOR GOALS HAS BEEN TO MINIMIZE YEAR-TO-YEAR FLUCTUATIONS IN THE NUMBER OF NEW AND COMPETING RENEWAL GRANTS.

WHILE IT IS TRUE THAT NIH HAS SUPPORTED AT LEAST 5,000 SUCH GRANTS EACH YEAR SINCE 1980--AND IN 1984 THE TOTAL IS EXPECTED TO BE 5,272--IT WOULD BE INCORRECT TO CONTEND THAT MAINTENANCE OF THIS NUMBER PER SE HAS PRODUCED STABILITY FOR THE BIOMEDICAL RESEARCH ENTERPRISE OVERALL. THE FACT THAT WE HAVE FOUND IT NECESSARY TO FUND RESEARCH PROJECT GRANTS AT SUPPORT LEVELS BELOW THOSE RECOMMENDED BY PEER REVIEWERS IS A CHRONIC SOURCE OF CONCERN TO ALL INVOLVED. MOREOVER, REPEATED AND UNPREDICTABLE REDUCTIONS IN THE FRACTION OF TOTAL NIH DOLLARS AVAILABLE FOR ALL OTHER FUNDING MECHANISMS, INCLUDING TRAINING AND RESEARCH CAREER AWARDS, RESEARCH CENTERS AND CONTRACTS, HAS LED TO LESS THAN DESIRABLE LEVELS OF EFFORT IN THESE ESSENTIAL COMPLEMENTARY AREAS.

THOSE OF YOU WHO HAVE KEPT IN TOUCH WITH THE NIH BUDGET OVER A PERIOD OF YEARS KNOW THAT EVEN THOUGH IN THE LONG TERM THE INCREASE HAS BEEN SPECTACULAR, THE RATE OF GROWTH FOR THE PAST DECADE HAS BARELY KEPT PACE WITH INFLATION. Slide I

AS EARLY AS 1974, THE NIH HAD BEGUN ACCOMMODATING TO A RELATIVELY CONSTANT BUDGET BY SHIFTING FUNDS AMONG ITS VARIOUS SUPPORT MECHANISMS SO THAT IT COULD AWARD MORE PROJECT GRANTS IN RESPONSE TO AN INCREASING NUMBER OF EXCELLENT INVESTIGATOR-INITIATED APPLICATIONS. THE NEED FOR SUCH SHIFTS HAS BEEN HEIGHTENED BY OUR EFFORTS TO ASSURE THAT 5,000 NEW AND COMPETING GRANTS WOULD BE AWARDED EACH YEAR.

Slide II

DESPITE THESE UNTOWARD SIDE EFFECTS OF THE RECENT PARTIAL IMPLEMENTATION OF A STABILIZATION POLICY, THE NIH HAS NO DESIRE TO ABANDON THE CONCEPT, AND WE RECOGNIZE THE POSITIVE EFFECT OF EVEN AN INCOMPLETE APPLICATION OF THIS LONG-RANGE PLAN DURING A TIME OF FISCAL STRINGENCY. IT IS OUR CONVICTION THAT THE IMPORTANT NEEDS ADDRESSED BY THE ORIGINAL STABILIZATION PLAN REMAIN, AND THAT THE ESSENTIAL COMPONENTS OF THE STRATEGY CONTINUE TO BE VITAL AS A MEANS FOR ADDRESSING THOSE NEEDS.

THE 1985 BUDGET REQUEST PROVIDES FOR THE SUPPORT OF 9,000 RESEARCH TRAINEES, A REDUCTION OF ABOUT 9 PERCENT FROM THE ESTIMATED 1984 LEVEL OF 9,863, BUT IT INCLUDES FUNDS FOR A 5 PERCENT INCREASE IN THE STIPEND LEVELS.

OVER THE PAST FIVE YEARS, THE NIH HAS SUPPORTED AN AVERAGE OF 10,600 TRAINEES PER YEAR, A NUMBER THAT REPRESENTS 98 PERCENT OF THE LEVEL RECOMMENDED BY THE NATIONAL ACADEMY OF SCIENCES. HOWEVER, THE TREND IS DOWNWARD. IN 1980, THE BUDGET FOR TRAINING WAS JUST OVER 5 PERCENT OF THE TOTAL NIH BUDGET. BY 1984, TRAINING'S SHARE OF THE BUDGET HAD BEEN REDUCED TO 3.7 PERCENT, AND THE 1985 SHARE OF THE REQUEST FOR TRAINING IS SLIGHTLY LOWER THAN LAST YEAR.

WE ARE CONCERNED ABOUT THE NEED TO SUPPORT THE MOST PROMISING YOUNG PEOPLE WITH THE BEST POSSIBLE TRAINING MECHANISMS TO EQUIP THEM TO CARRY OUT RESEARCH MISSIONS IN THE

YEARS TO COME. WITH THE HELP OF OUR PRINCIPAL ADVISORY GROUPS, THE SENIOR STAFF OF THE NIH DURING THE COMING YEAR WILL GIVE CONSIDERATION TO A NUMBER OF KEY QUESTIONS REGARDING OUR TRAINING PROGRAMS. FOR EXAMPLE, SHOULD THE SIZE OF OUR MANPOWER DEVELOPMENT PROGRAMS BE TIED TO OUR ESTIMATES OF FUTURE LEVELS OF PUBLIC SUPPORT FOR HEALTH RESEARCH? IS THERE AN OPTIMUM LEVEL OF INVESTMENT IN TRAINING?

ONE OF THE ISSUES FOR CONSIDERATION IS OF SPECIAL INTEREST TO INSTITUTIONS ENGAGED IN OUR TRAINING PROGRAMS. IT IS THE BASIC CONSIDERATION, "WHAT ARE THE ELEMENTS THAT LEAD TO THE PRODUCTION OF SUCCESSFUL INVESTIGATORS?" THE RESEARCH ENVIRONMENT IS BECOMING TECHNOLOGICALLY EVER MORE COMPLEX. ARE WE ENCOURAGING NEW CLINICAL INVESTIGATORS, FOR EXAMPLE, TO SEEK ENOUGH RESEARCH TRAINING AND EXPERIENCE IN THIS KIND OF AN ENVIRONMENT TO EXPECT THEM TO COMPETE SUCCESSFULLY IN RESEARCH GRANT PROGRAMS, PARTICULARLY THOSE OF THE NIH? SHOULD WE EXAMINE THE KIND OF TRAINING THEY ARE RECEIVING AND THE CHARACTERISTICS OF THE MOST EFFECTIVE TRAINING PROGRAMS?

WE ARE ADDRESSING THE QUESTION OF A PROPER MIX OF MANPOWER DEVELOPMENT PROGRAMS. WE SUPPORT PREDOCTORAL STUDENTS, POSTDOCTORAL FELLOWS, AND TRAINEES. SOME MECHANISMS MAY BE SERVING OUR PURPOSES BETTER THAN OTHERS. SOME THAT WERE SUCCESSFUL 20 YEARS AGO MAY BE LESS SO TODAY.

AT THIS POINT, IT IS MY VIEW THAT NIH SUPPORT FOR PRE-DOCTORAL TRAINING FOR THE PH.D. CANDIDATE IS HIGHLY DESIRABLE AND SHOULD BE CONTINUED. I AM DISAPPOINTED IN THE RESPONSE OF MEDICAL STUDENTS TO THE NEW EQUIVALENT TO OUR POSTSOPHOMORE FELLOWSHIPS. I THINK IT IS ESSENTIAL THAT YOUNG PEOPLE HAVE A CHANCE FOR GREATER EXPOSURE TO RESEARCH EARLY IN THEIR PRO-FESSIONAL TRAINING. WE WILL BE LOOKING FOR WAYS TO ATTRACT MORE STUDENTS INTO SUCH PROGRAMS.

FOR POSTDOCTORAL TRAINEES, THE INDICES OF SUCCESS OF PH.D.S WHO HAVE BEEN ON TRAINING GRANTS OR FELLOWSHIPS ARE GOOD. OUR POSTDOCTORAL FELLOWSHIPS FOR M.D.S HAVE BEEN QUITE PRODUCTIVE, BUT TRAINING GRANTS FOR M.D.S LESS SO. PROBLEMS INCLUDE THE LENGTH OF TRAINING, THE INTENSITY OF TRAINING, AND ITS ULTIMATE GOALS. ONE COMPLICATING FACTOR HERE IS THE RELA-TIONSHIP OF RESEARCH TRAINING TO SPECIALTY BOARD REQUIREMENTS. THIS PROGRAM WILL REQUIRE CAREFUL EXAMINATION.

OUR TWENTY-YEAR-OLD PROGRAM FOR COMBINED M.D./PH.D. STUDENTS, KNOWN AS THE MEDICAL SCIENCE TRAINING PROGRAM, HAS BEEN QUITE SUCCESSFUL.

THE STIPEND ISSUE REMAINS A VEXING QUESTION, PARTICULARLY THE ISSUE OF WHAT SHOULD BE DONE ABOUT STIPENDS FOR PRE-DOCTORAL TRAINEES.

PERMIT ME TO TURN NOW TO A SUBJECT THAT DR. LIGHTFOOT ASKED ME TO DISCUSS BRIEFLY. IT INVOLVES THE CONGRESS BUT NOT THE APPROPRIATION COMMITTEES AT THIS TIME. I AM SPEAKING OF PENDING LEGISLATION FOR THE CREATION OF NEW INSTITUTES, PARTICULARLY THE PROPOSED NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES. AS YOU PROBABLY KNOW, THE NIH AND THE DEPARTMENT OF HEALTH AND HUMAN SERVICES HAVE OPPOSED THIS LEGISLATION. OUR OPPOSITION IS BASED NOT ONLY ON ITS PREDICTABLY ADVERSE EFFECT ON ADMINISTRATIVE COSTS AND FLEXIBILITY, BUT ALSO BECAUSE MORE COMPARTMENTALIZATION IS COUNTER TO THE DIRECTION IN WHICH SCIENCE IS MOVING.

THE STATUS OF ARTHRITIS RESEARCH WITHIN THE NIH IS ITSELF A GOOD ILLUSTRATION OF THE INTERDISCIPLINARY EFFORTS CHARACTERISTIC OF TODAY'S RESEARCH. IT IS NO SURPRISE THAT THE LARGER SHARE OF SUPPORT FOR RESEARCH ON THE CAUSES, PREVENTION, AND CONTROL OF ARTHRITIS IS PROVIDED BY THE NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES. BUT 10 OF THE 12 NIH UNITS THAT FUND RESEARCH ARE CURRENTLY SUPPORTING RESEARCH ON ARTHRITIS AND RELATED MUSCULOSKELETAL DISEASES.

OF THE MORE THAN $80 MILLION TO BE EXPENDED BY THE NIH ON ARTHRITIS THIS YEAR, THREE-FOURTHS WILL COME FROM NIADDK. THE

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, HOWEVER, WILL SPEND MORE THAN $10 MILLION ON RHEUMATIC DISEASES. IN FACT, EIGHT OF OUR FUNDING UNITS EACH EXPECT TO EXCEED A MILLION DOLLARS FOR ARTHRITIS-RELATED RESEARCH IN FISCAL 1984.

THE LACK OF A DEDICATED INSTITUTE APPEARS NOT TO HAVE IMPEDED THE FUNDING OF ARTHRITIS-RELATED PROGRAMS, FOR WHICH THE RATE OF GROWTH EXCEEDS THAT EXPERIENCED BY ALL OF OUR OTHER MAJOR PROGRAMS. SINCE 1980, ARTHRITIS EXPENDITURES HAVE INCREASED BY MORE THAN 50 PERCENT. THAT IS NEARLY TWICE THE INCREASE IN THE TOTAL NIH BUDGET DURING THE SAME PERIOD.

ANOTHER INDICATION OF THE VITALITY OF THE ARTHRITIS PROGRAM IS THE ESCALATION IN THE NUMBER OF APPLICATIONS FOR INVESTIGATOR-INITIATED RESEARCH PROJECT GRANTS. IN 1978, 97 SUCH APPLICATIONS WERE RECEIVED BY THE NIH AND FROM THEM 30 NEW AND COMPETING AWARDS WERE MADE. BY 1983, THE NUMBER OF APPLICATIONS HAD DOUBLED AND 61 AWARDS WERE MADE.

IN EXPRESSING OUR OPPOSITION TO THE CREATION OF NEW INSTITUTES, I AM AWARE THAT ADAMANT REFUSAL ON THE PART OF AN ORGANIZATION LIKE OURS TO CONSIDER CHANGE IS SHORTSIGHTED.

SUCH A POSTURE IGNORES THE HISTORY OF THE DEVELOPMENT OF THE NIH--INSTITUTE-BY-INSTITUTE--AND MOST OF THEM ARE DISEASE ORIENTED. IT WAS FROM SUCH SPECIFICITY THAT PUBLIC INTEREST AND VIGOROUS SUPPORT WAS DRAWN.

OUR ATTITUDE MUST NOT BE THE SAME AS THAT OF THE BOSTON WOMAN THAT DANIEL BOORSTIN WROTE ABOUT IN HIS LATEST BOOK. SHE WAS A MEMBER OF AN OLD NEW ENGLAND FAMILY WHO WAS ASKED WHY SHE NEVER TRAVELED. "WHY SHOULD I?" SHE REPLIED, "I'M ALREADY THERE."[4]

IN JUNE OF LAST YEAR, WE ASKED THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES TO MAKE AN OBJECTIVE STUDY OF THE ORGANIZATIONAL STRUCTURE OF THE NIH AND, CONSIDERING SCIENTIFIC DEVELOPMENTS AND ECONOMIC CONDITIONS, TO RECOMMEND THE ESTABLISHMENT OF STANDARDS FOR DETERMINING THE NEED FOR ANY SUBSTANTIAL CHANGE IN THE ORGANIZATIONAL STRUCTURE OF THE AGENCY. WE EXPECT THE STUDY TO BE COMPLETED AND TO HAVE A REPORT FROM THE IOM IN NOVEMBER OF THIS YEAR.

ANOTHER LEGISLATIVE ISSUE OF SUBSTANTIAL IMPORTANCE TO THE ENTIRE RESEARCH COMMUNITY CONCERNS RESTRICTIONS ON THE USE OF LABORATORY ANIMALS. CURRENTLY, THERE ARE AT LEAST SEVEN SUCH MEASURES BEFORE THE CONGRESS, SOME OF WHICH COULD BRING ESSENTIAL CATEGORIES OF RESEARCH TO A VIRTUAL STANDSTILL. ADDITIONALLY, SOME 69 PROPOSED NEW STATUTES OF VARYING

DEGREES OF SEVERITY HAVE BEEN INTRODUCED OR HAVE BEEN ENACTED IN 17 STATES. IT SEEMS CLEAR THAT PUBLIC SUPPORT FOR LABORATORY EXPERIMENTS INVOLVING ANIMALS MAY BE ERODING. MANY CRITICS--SOME OF WHOM ARE ATTACKING BIOMEDICAL RESEARCH INVOLVING ANIMALS AS BOTH INHUMANE AND UNNECESSARY--ARE POLITICALLY SOPHISTICATED AND SINCERE IN THEIR OPPOSITION. IT IS INCUMBENT ON US ALL TO DO A BETTER JOB OF EXPLAINING THE NEED FOR ANIMAL STUDIES. THERE IS A TENDENCY ON THE PART OF THE HEALTH RESEARCH COMMUNITY TO TAKE IT FOR GRANTED THAT THE GENERAL PUBLIC SHARES OUR UNDERSTANDING OF THE CRITICAL NEED FOR USING LABORATORY ANIMALS IF PROGRESS IN BIOMEDICAL RESEARCH IS TO CONTINUE.

WE NEED TO MAKE SURE THAT THE PUBLIC UNDERSTANDS THAT VIRTUALLY EVERY MAJOR MEDICAL ADVANCE IN THIS CENTURY HAS DEPENDED UPON ANIMAL EXPERIMENTATION, AS VIVIDLY ILLUSTRATED BY THE HISTORY OF PROGRESS AGAINST SUCH DISORDERS AS HEART DISEASE, CANCER, KIDNEY DISEASE, HEPATITIS, AND POLIO. AT THE SAME TIME, WE MUST DEMONSTRATE OUR OWN ALLEGIANCE TO THE MORAL IMPERATIVE THAT ANIMAL EXPERIMENTATION BE DONE IN THE MOST HUMANE, CONSERVATIVE AND EFFECTIVE MANNER.

WHILE IT IS TRUE THAT COMPUTER MODELING AND <u>IN VITRO</u> PROCEDURES MAY EVENTUALLY REDUCE THE NUMBER OF ANIMALS USED IN SOME TOXICOLOGICAL TESTING, THE INVOLVEMENT OF ANIMALS TO

DETERMINE THE RESPONSE OF BIOLOGICAL SYSTEMS AND ORGANISMS TO CAREFULLY MEASURED INTERVENTIONS IS AND WILL REMAIN CENTRAL TO THE RESEARCH ENTERPRISE.

A COMPREHENSIVE EDUCATION PROGRAM IS BEING LAUNCHED BY THE NIH OFFICE FOR PROTECTION FROM RESEARCH RISKS WITH THE PURPOSE OF BUILDING A BROADER CONSENSUS AMONG SCIENTISTS AND THE PUBLIC CONCERNING POLICIES FOR THE HUMANE CARE AND USE OF RESEARCH ANIMALS.

THIS PROGRAM WILL BE INAUGURATED APRIL 11 WITH A NATIONAL SYMPOSIUM TO BE HELD AT THE NATIONAL ACADEMY OF SCIENCES. THE SUBJECT WILL BE "IMPERATIVES IN RESEARCH ANIMAL USE: SCIENTIFIC NEEDS AND ANIMAL WELFARE." PROMINENT RESEARCHERS, CLINICIANS, AND ANIMAL CARE EXPERTS, AS WELL AS LEADERS OF ANIMAL WELFARE ORGANIZATIONS WILL PARTICIPATE IN TWO DAYS OF INTENSIVE DISCUSSIONS ON THE MANY ISSUES IN THE CONTEXT OF THE PUBLIC HEALTH SERVICE POLICIES AND PROCEDURES FOR HUMANE CARE AND USE OF LABORATORY ANIMALS.

A SERIES OF REGIONAL WORKSHOPS WILL BE HELD COVERING ESSENTIALLY THE SAME SUBJECT MATTER AS THAT TO BE ADDRESSED BY THE NATIONAL SYMPOSIUM, BUT WITH SPECIAL EMPHASIS ON THE RESPONSIBILITIES OF ACADEMIC AND OTHER INSTITUTIONS WHERE RESEARCH IS CONDUCTED WITH FEDERAL SUPPORT.

A GUIDEBOOK WILL BE PREPARED FOR USE BY INSTITUTIONAL ANIMAL RESEARCH COMMITTEES, INSTITUTIONAL ADMINISTRATORS AND INVESTIGATORS TO PROMOTE THEIR UNDERSTANDING OF THEIR RESPONSIBILITIES IN CARRYING OUT THE PHS ANIMAL WELFARE POLICY.

AUDIOVISUAL MATERIALS AS WELL AS PRINTED INFORMATION WILL BE PREPARED FOR USE IN INCREASING PUBLIC UNDERSTANDING OF THE NEEDS FOR ANIMAL RESEARCH AND OF THE SAFEGUARDS IN PLACE TO ASSURE THEIR PROPER AND HUMANE USE.

THE FEDERAL GOVERNMENT CANNOT ON ITS OWN DEAL ADEQUATELY WITH THE MOUNTING PRESSURE ON THIS ISSUE. IT IS THE RESPONSIBILITY OF THE INSTITUTIONS AND THE INVESTIGATORS INVOLVED TO BECOME MORE ACTIVE IN RESPONDING TO QUESTIONS ABOUT THE NEED FOR ANIMALS IN RESEARCH AND ABOUT THE APPROPRIATE SAFEGUARDS. THEY SHOULD BE FAMILIAR WITH THE GUIDELINES AND POLICIES, LOCAL AND NATIONAL, THAT APPLY; THEY SHOULD BE WILLING TO ARTICULATE THE BENEFITS THAT HAVE ACCRUED TO MEDICINE FROM THE USE OF ANIMALS. THOSE WHO ACTUALLY CONDUCT RESEARCH SHOULD BE WILLING AND ABLE TO EXPLAIN CLEARLY WHY A PARTICULAR EXPERIMENT IS IMPORTANT AND WHY ANIMALS ARE ABSOLUTELY NECESSARY IN A GIVEN EXPERIMENT.

ANY DISCUSSION OF BIOMEDICAL RESEARCH AT THIS TIME WOULD BE INCOMPLETE WITHOUT A MENTION OF THE RECENT PACE OF DISCOVERY, ESPECIALLY IN THE REALM OF MOLECULAR BIOLOGY. EXPLOITATION OF OUR RAPIDLY EXPANDING KNOWLEDGE IN THIS FIELD IS

OPENING NEW VISTAS FOR IMPROVEMENTS IN PREVENTION, DIAGNOSIS AND TREATMENT OF MANY DISEASES. AND EVEN MORE EXCITING ARE THE TANTALIZING INSIGHTS GAINED FROM THE USE OF THE NEW TECHNIQUES IN THE STUDY OF DISORDERS RANGING FROM CANCER TO HUNTINGTON'S DISEASE.

NOBELIST ARTHUR KORNBERG USED AN UNUSUAL BUT APT METAPHOR TO DESCRIBE THE CURRENT SITUATION. "MOLECULAR BIOLOGY," HE SAID, "HAS SUCCESSFULLY BROKEN INTO THE BANK OF CELLULAR CHEMISTRY, BUT FOR THE LACK OF BIOMEDICAL TOOLS AND TRAINING, IS STILL FUMBLING TO UNLOCK THE MAJOR VAULTS."[5] ALTHOUGH AS YET THEY ARE IMPERFECTLY UNDERSTOOD, THE RECENTLY DISCOVERED AND APPLIED TECHNIQUES HAVE BEEN RESPONSIBLE FOR SIGNIFICANT DEVELOPMENTS WITH GREAT PROMISE FOR THE IMPROVEMENT OF HEALTH. AT THE SAME TIME, THEY HAVE LED TO THE CREATION OF TOTALLY NEW INDUSTRIES. RECENTLY, THE CONGRESSIONAL OFFICE OF TECHNOLOGY ASSESSMENT RELEASED A COMPREHENSIVE ANALYSIS OF COMMERCIAL BIOTECHNOLOGY.[6] FROM ITS EXHAUSTIVE STUDY, THE OTA CONCLUDED THAT THE UNITED STATES HAS A COMMANDING LEAD WORLDWIDE IN THE DEVELOPMENT AND APPLICATION OF THE NEW BIOTECHNOLOGY. THE STUDY POINTED OUT THAT THE PRIVATE SECTOR IN THIS COUNTRY INVESTED MORE THAN A BILLION DOLLARS IN 1983 TO COMMERCIALIZE RECOMBINANT DNA, CELL FUSION, AND OTHER RELATED TECHNOLOGIES THAT WERE DEVELOPED WITH PUBLIC FUNDS DIRECTED TOWARD BIOMEDICAL RESEARCH. MOST OF THE BASIC RESEARCH LEADING TO THESE DEVELOPMENTS WAS CONDUCTED BY OR SUPPORTED THROUGH THE NIH.

AN ESSENTIAL FACTOR IN THIS SPECTACULAR ADVANCE AND ONE ON WHICH FUTURE GROWTH WILL DEPEND IS THE AVAILABILITY OF MANY YOUNG SCIENTISTS TRAINED BY THE NIH.

IN THIS CONNECTION, I SHOULD NOTE CURRENT DEVELOPMENTS THAT ARE INCREASINGLY AFFECTING THE LONG-STANDING FEDERAL-ACADEMIC PARTNERSHIP. RECENTLY, WE HAVE SEEN THE BEGINNINGS OF A THREE-WAY PARTNERSHIP INVOLVING INDUSTRY AS A PARTICIPANT. THERE HAVE BEEN SUGGESTIONS THAT THE NIH TAKE SOME KIND OF ACTIVE PART IN THE INSTITUTION OF THESE NEW RELATIONSHIPS. WE HAVE NOT DONE SO. WE BELIEVE IT PREFERABLE THAT THE NEW FORMS OF JOINT ENDEAVOR CONTINUE TO EVOLVE AS THEY HAVE BEEN WITH THE GOVERNMENT PLAYING A FACILITATIVE ROLE. NOTWITHSTANDING THE FACT THAT THE AREAS OF COLLABORATION BETWEEN THE UNIVERSITIES AND INDUSTRY HAVE BROADENED SIGNIFICANTLY AND PROMISE TO CONTINUE IN THAT EXPANSION, I BELIEVE IT SAFE TO PREDICT THAT THE GOVERNMENT WILL CONTINUE AS THE PRINCIPAL SOURCE OF FUNDING FOR BASIC RESEARCH.

GEORGE KEYWORTH HAS COMMENTED THAT ". . . IN SPITE OF INDUSTRY'S INCREASED SPENDING FOR ITS OWN RESEARCH AND DEVELOPMENT, WE HAVE NO ILLUSIONS THAT THE PRIVATE SECTOR IS GOING TO RELIEVE THE FEDERAL GOVERNMENT OF ITS RESPONSIBILITIES FOR THE SUPPORT OF BASIC RESEARCH." HE FORTIFIED THAT POINT BY ADDING FURTHER THAT "THERE IS NO QUESTION THAT STABLE FUNDING FOR BASIC RESEARCH HAS TO BE A HIGH PRIORITY FOR ALL OF US."[7]

IN COMMENTING ON THE ROLE OF BASIC RESEARCH, LEWIS THOMAS ALSO USED A BANKING METAPHOR, A BIT LESS FELONIOUS THAN THAT EMPLOYED BY ARTHUR KORNBERG. HE SAID, "WE ARE BEGINNING TO DRAW FROM A BANK OF STORED INFORMATION IN BIOMEDICAL SCIENCE." HE WARNED, "THERE IS SOME DANGER THAT THE NEED TO CONTINUE DEPOSITING NEW INFORMATION IN THAT BANK WILL BE OVERLOOKED IN THE PRESSURE FOR QUICK APPLICATION."[8]

HIS ARGUMENT, WITH WHICH I TOTALLY AGREE, IS THAT WE MUST CONTINUE TO GAMBLE ON IMAGINATIVE IDEAS THAT HAVE A HIGH PROBABILITY OF NOT TURNING OUT AS PREDICTED--THAT WE MUST BE WILLING TO RUN THE RISK OF BEING WRONG. OTHERWISE, AS HE SAID, "THE COUNTRY'S BASIC SCIENCE EFFORT WILL COME TO A STANDSTILL AND THE BANK WILL GO EMPTY."

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[1]GEORGE KEYWORTH, "FEDERAL R&D AND INDUSTRIAL POLICY," SCIENCE, JUNE 10, 1983, P. 1123.

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[3]FROM NIH ALMANAC 1983, DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLICATION NIH-83-5, MARCH 1983, P. 121.

[4]DANIEL J. BOORSTIN, THE DISCOVERERS, RANDOM HOUSE, NEW YORK, 1983, P. 179.

[5]ARTHUR KORNBERG, FROM AN UNPUBLISHED MANUSCRIPT, "UNDERSTANDING LIFE AS CHEMISTRY," 1982.

[6]COLIN NORMAN, "AMERICA DOMINATES IN BIOTECHNOLOGY," SCIENCE, FEBRUARY 4, 1984.

[7]KEYWORTH, "FEDERAL R&D AND INDUSTRIAL POLICY," SCIENCE, JUNE 10, 1983, P. 1124.

[8]LEWIS THOMAS, "ON SCIENCE BUSINESS," NEW ENGLAND JOURNAL OF MEDICINE, JANUARY 17, 1980, P. 157.

OPENING REMARKS*

by
James B. Wyngaarden, M.D.**

Good morning. I wish to echo the greetings extended to all of you by Dr. Brandt. I welcome all of you to the National Institutes of Health (NIH) Symposium on Imperatives in Research Animal Use. This Symposium and the educational programs that will follow in the months to come rank among the most important initiatives that NIH is undertaking this year.

Despite impressive progress in the prevention, diagnosis and treatment of disease in recent decades, important areas of biological understanding remain to be uncovered. If we are to exploit our research opportunities, involvement of laboratory animals must be integral to research now and in the foreseeable future.

While it is true that computer modeling and other procedures can be applied *in vitro* to reduce the number of animals required for certain kinds of toxicological testing, the involvement of animals to demonstrate the response of biological systems and organisms to carefully measured interventions *in vivo* is and will remain central to the research enterprise.

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*Presented at the National Symposium on Imperatives in Research Animal Use: Scientific Needs and Animal Welfare held at the National Academy of Sciences, Washington, D.C., on April 11, 1984, and sponsored by the National Institutes of Health.

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The question has been asked, "Who is to decide if a particular research project is important enough to warrant the use of animals and who determines the most appropriate animal model?" For traditional NIH project grants, the short answer is: the initial decision about the need and about the appropriate animal model for a specific project is made by the applicant-investigator. That decision, however, is subjected to repeated independent examination as the grant application winds its way through the NIH review process.

Before the application leaves the grantee institution, the principal research administrators, often with the advice of Animal Research Committees, must approve the proposal. Important considerations in that institutional review include the choice of the animal model, the number to be used, and the procedures proposed to make certain that the planned research can be carried out within the assurances that the institution has given the NIH regarding the care and use of research animals.

When any application for research involving vertebrates reaches the NIH, our study sections and other initial evaluation groups are required to critique (a) the appropriateness of the species of animals used, (b) the appropriateness of the number of animals used, (c) the care of animals before during, and after experimental procedures, and (d) any other information that has significance for the care and treatment of animals.

If problems or questions regarding the proposed use of animals are identified, the review group flags the application for further consideration and judgment by the cognizant staff. If the review group is satisfied that the choice and proposed use of the animals appear to be appropriate, a statement to that effect must also be included in the evaluation of the grant application. No award can be made unless the applicant institution has given the NIH Office for Protection from Research Risks an acceptable assurance of compliance with the Public Health Service (~~PHS~~) Animal Welfare Policy and all questions raised by the initial review groups have been resolved to the satisfaction of the NIH.

NIH has exhibited leadership in this field since 1963, and I am pleased to be part of its continuing efforts to provide for humane care and use of animals while advancing our ability to prevent and cure diseases for animals as well as human beings.

It is a matter of deep concern that public support for laboratory experiments involving animals may be eroding in spite of PHS responses to legitimate concerns about the use of animals in research. The critics of the PHS policies--some of whom are attacking biomedical research on animals as not only inhumane but unnecessary--appear to be sincere and politically sophisticated. It is therefore incumbent on us to strive to build a wider consensus concerning the policy for humane care and use of laboratory animals and to initiate vigourously procedures to ensure that our policies will be implemented.

Consequently, for its part, NIH has recently taken a number of actions and has additional plans for future steps in development.

NIH has completed site visits to ten randomly selected institutions receiving support from NIH to conduct research that involves animals. A report on the site visits, which has recently been released, should help us further strengthen the system by which NIH assures that animals in research are adequately protected. It will also affect PHS policy for the care and use of animals. The proposed PHS Policy on Animal Welfare, released in the same issue of the NIH Guide for Grants and Contracts as the site visit report, will be discussed later in the program. Public comment regarding this important document is encouraged.

In summary, NIH has taken leadership to develop better understanding and implementation of the PHS Policy on Animal Welfare. It has conducted site visits to evaluate the efficacy of the present system and to determine how best to improve it. It is in the process of revising and strengthening its policies.

But the Federal Government cannot on its own adequately deal with the mounting pressure on this issue. It is the responsibility of the institutions and the investigators involved to become more active in responding to questions about the need for animals in research and appropriate safeguards. They should be familiar with the guidelines and

policies, local and national, that apply; they should be willing to articulate the benefits that have accrued to medicine because of animal participation in research. Those who actually conduct research involving animals should be willing and able to explain clearly why a particular experiment is important and why animals are absolutely necessary in the given experiment.

I hope that these issues, and others as well, will be advanced as this symposium unfolds.

INTRODUCTORY REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

I would like to thank Professor Turano and Professor Gorini, the World Health Organization, and especially the Menarini Foundation for the high privilege of attending this International Conference and the opportunity to make a few introductory remarks. This is my first visit to Cremona, as I suspect it is for many of us. What an excellent choice it is for a conference of this type. The name Cremona is synonymous with the enduring value of outstanding achievement, in this instance particularly in the construction of the violin. The tradition established by the Amati family as transmitted to Stradivarius and Guarnieri has given us priceless instruments that remain the best in the world. It is a daunting challenge to the speakers of this conference to attain that same level of performance.

Much of today's cultural and scientific world has emerged from the social experiments of thinkers, artists, and investigators caught up in the ferment of Renaissance Italy. Much of the drama of that period in history was played out nearby.

With a radius of less than 120 miles, a circle centered at Cremona would encompass Europe's first university at Bologna that started teaching in the 11th century and opened Europe's first medical faculty in 1156. The same circle would enclose the birthplace of Dante, of Leonardo da Vinci, of Galileo, the studios of Michelangelo and Raphael and Donatello, and the large, prosperous and independent city states of Milan, Florence, Pisa, and Venice.

I make a point of mentioning this historical context because we are currently in the midst of another period of intellectual ferment. This is a time of unparalleled growth of knowledge in the science of biology. The surge of discovery in the biosciences is without precedent and is still gathering strength. It is a time of explosive advance and refinement of information. An enormous increase in the power of experimental techniques is now producing answers to complex, long-standing biological questions. Oncology and

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**Director, National Institutes of Health, Bethesda, MD.

indeed all biomedical science have gone molecular. After centuries of varying and often opposing theories and hypotheses on the cause and nature of cancer, we are beginning to uncover the cellular structures and mechanisms related to tumor growth. Twentieth century molecular biology has now given credence to the long-sought link between viruses and cancer.

But as those of you who have been working in this field are fully aware, the course of this progress has not been smooth and uneventful. Dr. Robert Gallo spoke from such a perspective when he presented the 1983 Dyer lecture last fall at the NIH. He reminded us that in the mid-70s, "Many of us that were close to the field might say that tumor virology, if anything, was on the downswing with criticisms and feelings of disappointment within and outside of the field." He told of "beginning doubts about how applicable tumor virology would be for understanding human cancer or if it would ever be applied in any way to human cancer."

But then he was able to make the observation that "five to ten years later, we are no longer at the threshold--perhaps we are in the midst of a new biological, scientific era--and we can say that viral oncology or tumor virology is right in the center."

The former NIH Deputy Director for Science, DeWitt Stetten, Jr., has recently edited an historical account of intramural research at the National Institutes of Health. Two chapters in this forthcoming book are devoted to the subject of this meeting. One is titled "Viral Oncology," and the other "Virogenes to Oncogenes." Dr. Stetten's introduction to the chapter on viral oncology reflects the considered view of a senior scientist not directly involved in research on viral oncology. In his introductory paragraphs, Dr. Stetten takes note of a most significant fact--that persistent interest in the mechanism of cancer causation has resulted in a vigorous stimulation of such fields as virology, immunology, and molecular biology.

He then gave a thumbnail sketch of the history of viral oncology. "The quest for a cancer virus," he said, "started with the simplistic notion that cancer was like a number of other viral diseases in being the result of a specific infection by a specific agent. Indeed, a number of animal models supported this view. Beginning early in this century, identification of viruses as tumorigenic agents in a wide variety of animals led to expectations of an ultimate isolation of 'the virus of human cancer.' In preparation for this event, NIH constructed a suitable edifice to house the formidable organism. Building 41, completed in 1969, included sophisticated devices for viral containment. But the virus of human cancer has not

been found. Building 41 is now occupied by worthy scientists who perform other worthy experiments. Some of its features were put to explicit use when the development of recombinant DNA technology called for high-containment conditions.

"With the passage of time, other etiologies of cancer have come to the fore. Many human cancers are attributable to nonliving environmental agents such as cigarette smoke, asbestos, sunlight, ionizing radiation, and a number of well-identified organic molecules. While these have seized center stage, one glimpses in the wings still other suspects, including dietary and genetic factors. One of these . . .is the oncogene, a factor conceived as a gene of viral origin, perhaps the illusive 'common denominator' of cancer causation. The study of virus will continue to play an important role in cancer etiology," he said.

Permit me to underline the observation by Dr. Stetten that research on cancer causation has stimulated many fields of biomedical research. Movement in this field has been a cause--an effect--and a part of the whole forward sweep, just as the array of specific elements of progress in the arts and sciences became both cause and effect of the Renaissance.

In Dr. Gallo's lecture from which I quoted earlier, he mentioned that one of the reasons for the recent and rapid emergence of tumor virology is that molecular biologists used tumor viruses in many different lines of investigation. As Dr. Gallo put it, "the tumor viruses were used almost as a playground for unraveling some of the basic questions in molecular biology."

He noted that during the past decade more and more people learned about such viruses and appreciated their usefulness. Further, he stated that there was a growing realization that what came out of basic information from tumor viruses on the mechanisms of carcinogenesis--especially from work in vitro with adenoviruses, SV 40, polyoma and more recently papilloma viruses--was important and might be useful for studies in all fields of carcinogenesis. Manipulation of viruses, plus the tools of DNA recombinant technology, hybridization, and gene mapping have supplied researchers with much information as to the nature of oncogenes. As in so many areas of science, the mechanisms seem to grow more complicated the more we learn. Nevertheless, studies of viruses are our best hope for understanding in a fundamental way the basic defect that confers the neoplastic phenotype. The hope, of course, is that viral studies will have general significance to understanding even nonviral-caused tumors.

While my remarks have focused mostly on molecular happenings, it is also obvious that enormous advances have been made over the years in fundamental cancer research through epidemiologic studies. These international opportunities have sent scientists--including many from the NIH--to many parts of the world. Some of the major advances in viral oncology have also been the result of international collaborations. This meeting provides an opportunity to solidify some of these collaborative efforts and, it is hoped, stimulate additional joint inquiries.

I look forward to learning more about new developments in cancer virus research--especially the very fruitful work in E-B virus, papillomas, HTLV and hepatomas--during the next two days.

THE IMPORTANCE OF BIOMATERIALS RESEARCH TO IMPROVED HEALTH CARE*

by

James B. Wyngaarden, M.D.**

I am grateful for the invitation to deliver some remarks before this international conference and want to welcome you--especially the foreign visitors--to Washington during probably its finest time of year. As many of you know, the Washington, DC area is the home of a number of Federal agencies with a high level of interest in biomaterials research and development--the National Institutes of Health, the Food and Drug Administration, the National Bureau of Standards, and, perhaps to a lesser extent, the Veterans Administration, the Defense Department, the Department of Energy, and the Department of Transportation. Since coming to the National Institutes of Health as director two years ago today, I have attended many meetings and conferences discussing the ways and means of research rather than the substance of science. The prospect of greeting participants assembled for this meeting was a great attraction for me, especially since your work is so important to the accomplishment of the NIH mission--to improve the health of all through support of research on prevention, diagnosis and treatment of disease.

Scientists and practitioners involved in biomaterials research, development and application in the past 30 years or so have come to play an important role in the enhancement of health and well-being. Since the early 1950's, devices made with synthetic or natural biomaterials have been successfully introduced into the human body at an ever-increasing rate. Initially focused on life-threatening situations, the clinical use of biomaterials has been extended progressively to treatment or support of a vast array to bodily functions.

Having achieved a measure of success, biomaterials are now employed to address needs for rehabilitation, comfort, convenience, and aesthetics.

The number of biomaterial implants is estimated to be several million per year in the U.S. alone, for devices as varied as vascular grafts, intraocular lenses, cardiac pacemakers, hip prostheses, fracture plates, breast augmentations and dental implants. So-called "spare parts" medicine, first made possible by the availability of materials of industrial origin and presented as a therapeutic approach in end stage disease, is now shifting toward elective restoration of chronically damaged structures, and may some day be considered for preventive maintenance in early-stage disease. Biomaterials are applied across the age spectrum--for example, it is now

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possible to implant shunts in utero, and the number of elderly people benefiting from intraocular lens implantation, dental devices, and artificial hips is increasing. Advances in the treatment of such chronic diseases as cancer and heart disease--plus the increasing numbers of old people in our population--will offer additional impetus to the development of devices requiring biomaterials. As more and more people are saved from death due to cancer, we will begin to seek better ways of rehabilitating them so they can carry out activities of daily living and of correcting or minimizing disfigurement due to their disease or its treatment. Part of this responsibility falls upon biomaterials experts. The fact that many people are now living into their 80's and even 90's, means that scientists and engineers will be faced with the challenge of providing materials and devices that might need to last in the body for 30 or 40 years rather than a mere 10.

The general public has so much optimism and faith about the accomplishments of science and technology that many of them assume that "spare parts" are available to correct almost every medical problem and to take over almost any bodily function. They know little of the scientific and developmental challenges that still remain in this area. L. L. Hench, of the Department of Materials Science and Engineering, University of Florida, writing in Science magazine described it well. He said, "The challenge of the field of biomaterials is that all implant devices replace living tissues whose physical properties are the result of millions of years of evolutionary optimization, and which have the capability of growth, regeneration, and repair. Thus, all man-made biomaterials used for repair or restoration of the body represent a compromise. The relative success or failure of a biomaterial reflects the scientific and engineering judgment used in achieving this compromise."[1]

These challenges were also addressed by a panel of experts who gathered at the NIH in 1982 for a consensus development conference on biomaterials. These experts pointed out the need for more basic research. While functional aspects of the performance of materials in the human body can be predicted with some reliability, forecasting the biological performance is difficult. There is limited fundamental information, they said, on the subtle variations of the host response to different classes, types, and forms of materials.

There is also a lack of understanding of the effects of the host tissue on the implant. The breadth and depth of knowledge regarding the host and biomaterials responses are inadequate because of the wide variety of implant materials, devices, anatomic sites, and duration of implantation. We simply do not yet know enough about the physicochemical phenomena at the tissue/biomaterial interface.

Likewise, the panel pointed out, little is known about the correlation between response in vivo and the test methods in vitro that are used initially to characterize the material biologically. To predict biological performance in the human, it is necessary to have a fundamental understanding of the dynamic biological changes occurring at the material/tissue interface. These include cell and molecular biology approaches to learn more about acute and chronic inflammatory responses, and how these responses may affect long-term

success or failure of the biomaterial. Thus, as a part of our fundamental knowledge, we will need to develop a more comprehensive appreciation of poorly understood areas such as infection, immune responses, and the characteristics of the tissue reaction at the blood/gas and blood/liquid interfaces.

There is also limited knowledge of the host response in different animal models. Variations in the response mechanisms among animal species and their similarities and dissimilarities with the human must be understood if animal experiments are to be appropriately interpreted. In addition, little has been done to identify precisely the etiology of device failure and the role that a material may or may not have played.

Looking at the challenge from a clinical perspective, the consensus panel pointed out some needs for new biomaterials: materials as permanent percutaneous implants without the risk of infection, materials for implants in the cardiovascular system without risk of blood clot formation; materials to duplicate the physical and biological properties of native tissue to replace skin, muscle, tendons; elastomers with extremely good flexure life and resistance to biodegradation; controlled biodegradable materials for use as sutures and blood vessel frameworks; materials with controlled physicochemical properties for use as drug delivery systems; small blood vessel substitutes; materials for soft tissue augmentation; materials for long-lasting prosthetic sphincters and bladders; and implant materials to prevent the loss of alveolar ridge in the elderly.

These are certainly formidable challenges to your community, especially given the economic realities that surround the development and actual marketing of such devices. But, there is reason for optimism.

The NIH has been and remains committed to the support and conduct of research relating to biomaterials and device development. Nearly every research component of NIH has such programs: the Eye Institute supports research on biomaterials for treatment of corneal disorders, on intraocular lenses, and on implants for use in retinal detachment surgery; the Dental Institute--though one of our smaller components--has a proportionally large extramural support program in biomaterials, aimed at endodontics, tooth implants, and prosthetic materials; the National Institute of General Medical Sciences, which for the most part supports basic research in biomaterials, has funded the exciting work at MIT on development of artificial skin for burn patients; the Heart, Lung, and Blood Institute has the largest commitment at NIH in biomaterials. Other relevant studies supported through NIH include those on implantable glucose sensors, programmable insulin delivery systems designed for external use; implantable prosthesis to replace the urinary bladder; cochlear implants; further improvement of percutaneous electrodes; and endoscopic instruments.

It is estimated that NIH support for biomaterial research will be approximately $53 million in FY 1985, up from about $48 million in FY 1983. And this does not include biomaterial work aimed at improving research tools. The 1985 figures would be divided approximately $26 million for basic studies, $21 million for applied work, and only $10 million for development.

The NIH, following its own historical bent and the more recent policies fostered by higher levels in the government, is committed strongly to support of basic research--including studies in the biomaterials area. Speaking about the priorities for the U.S. Federal Government support of research, George Keyworth, the President's Science Advisor, said, "We have no illusions that the private sector is going to relieve the Federal Government of its responsibilities for support of basic research."[2]

In the past several years, there has been heightened interest on the part of industry to increase and intensify their ties with universities and medical schools in the U.S. There is reason to believe that this new interest in collaborating in biotechnology would also extend to the biomaterials area. It has been estimated that sales in the U.S. annually from medical devices and diagnostic products is approximately $13.1 billion, a large figure compared with what is spent on biomaterials research. It is extremely promising to note that this meeting includes many representatives from industry, academia and government agencies.

I would like to mention two other matters that are important to the continued growth and accomplishment in your field: the public pressure regarding research in animals is growing in this country, and I understand that there are similar pressures elsewhere. Biomedical research cannot continue to progress without the use of laboratory animals. While it is true that alternative methods may eventually replace animals in some toxicological testing, the involvement of animals to demonstrate the response of intact biological systems and organisms to carefully measured interventions is and will remain central to the research enterprise. Virtually every major medical advance in this century has depended upon animal experimentations.

The possible erosion of public support for use of animals in research is a matter of deep concern. It is incumbent upon us scientists to strive to build wider consensus concerning the policy for humane care and use of lab animals. NIH, for its part, has recently taken a number of actions, including updating of our Guide for the Care and Use of Laboratory Animals, a major meeting held earlier this month in Washington, and a planned series of educational workshops for researchers and involved administrative staff at our grantee institutions. But the Federal Government cannot on its own adequately deal with the pressure. It is, I believe, the responsibility of institutions, investigators and professional societies, such as this, to become more active in responding to questions about the need for animals in research and appropriate safeguards. They should be willing to articulate the benefits that have accrued to medicine from involvement of animals in research. Those who actually conduct research involving animals should be able to explain clearly to the public why the animals are absolutely necessary in the given experiment and why the experiment itself is important.

Finally, as was pointed out at the NIH consensus development conference in 1982, there is a great need for additional communication in the biomaterials field. It is, of course, extremely useful that international meetings such as this one be held--members of each of the societies have much to contribute and much to learn from other members.

But there is an additional need, the consensus panel concluded, for groups of experts in various fields to work together in collaborations or in small workshops, for this kind of interaction is known to stimulate innovative and creative scientific projects.

This international meeting is also a large stride toward that objective.

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WELCOMING REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

It is a pleasure to extend to each of you a warm welcome to this testimonial dinner for our good friends, the Stadtmans. I am delighted to have this opportunity to add my words of appreciation and admiration for Terry and Earl. What a pleasure it is to join all of you in recognizing these two exemplars of the NIH ideal--two world-renowned scientists--two superb human beings.

Their commitment to intramural NIH began in 1950 when they came to Bethesda to join Jim Shannon at the National Heart Institute. The Stadtmans were in the vanguard of the migration of talented, well-trained and highly motivated young scientists who came to Bethesda to become a part of the new and powerful instrument for research being created here--the National Institutes of Health.

I first met Terry and Earl in 1953 when I came to the Heart Institute in a position roughly analogous to today's Clinical Staff Fellows, but the Clinical Center wasn't yet finished and I worked with Sid Udenfriend in Building 3. The Stadtmans were there then and already were held in special respect among the extraordinary talent in that building and at NIH.

For many of us, it was a period of advanced training--an opportunity to mature as scientists under optimal conditions--and then to move on to new responsibilities in academia or industry. But a substantial number of those who were attracted by the challenge stayed in Bethesda and--like the Stadtmans--have contributed immeasurably to the success of this unusual institution and, while doing so, have greatly influenced the lives and careers of more than a generation of associates, fellows, and other trainees who have come our way.

Association with active and demanding young scientists has no doubt helped to sustain their careers of research leadership and scientific productivity, as well as their youthful outlook and appearances. Tonight we honor the youthful Stadtmans for their accomplishments during a period of well over three decades--accomplishments that have won for

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*International Symposium on the Molecular Basis of Cellular Regulation, Clinical Center, National Institutes of Health, Bethesda, Maryland, May 3, 1984.

**Director, National Institutes of Health.

both of them election to the National Academy of Sciences, and for Earl, the President's Science Medal of Honor as well. They are scientists who have earned the ultimate accolade--the esteem and love of other scientists.

In honoring Terry and Earl, we are at the same time paying tribute to the people who have made intramural NIH so respected here. For the Stadtmans personify the qualities of dedication and rare ability that have been the essential ingredients of the intramural program.

In his foreword to the soon-to-be published book of essays on intramural NIH, assembled and edited by Hans Stetten, Dr. Lewis Thomas remarked that ". . . at the center of the NIH scientific effort, driving the whole vast enterprise along, is the research conducted on the Bethesda campus . . . for sheer excellence and abundant productivity, the institution cannot be matched by any other scientific enterprise anywhere."

He went on, ". . . One aspect of the intramural program deserves special mention and emphasis. It is as a training ground for young investigators . . . that the institution has achieved its most singular influence on the progress of American science.

"The NIH laboratories are something for the Government to boast about, to dine out on, and to be immensely proud of. It is my hope that the same intelligence and scientific good taste will be displayed for the institution's future as was used to build the magnificant instrument now at hand."

Our honorees, Terry and Earl, exemplify the intelligence and good scientific taste of which Lewis Thomas wrote.

Terry and Earl, -- we salute you!

NIH AND THE PRIVATE SECTOR--
NEW ROLES IN MEDICAL RESEARCH AND TRAINING*

by

James B. Wyngaarden, M.D.**

It is a pleasure to be here this evening to participate in honoring the five 1984 Pfizer postdoctoral fellows. I know that the five of you were successful in competition with over 140 nominees. I congratulate each of you.

I want to wish you the best as you begin a venture that will be exciting and full of new experiences. You are well equipped to begin what we confidently expect will be a fulfilling life-long commitment to biomedical research. You are fortunate to have arranged for research assignments, under preceptors who are preeminent in their fields, at medical schools where commitment to excellence in research and training is high.

Your preceptors also have much to gain from these relationships in the next three years. I know from experience how stimulating it can be to work with young people just entering the field of clinical research.

In addition, Pfizer is to be commended for establishing this postdoctoral fellowship program. They have taken a farsighted view. This new program is testimony to the company's interest in helping to provide for the future of biomedical science. I am pleased to be here this evening for an occasion that brings together representatives of the three major partners of the U.S. biomedical research enterprise.

Just five years ago, it was common to think of the biomedical research partnership as including the Federal Government and the academic world. This was due in large part to the relationships forged between academia and the Government during World War II. Following the war, the publicly and privately supported colleges and universities and research institutes were seen as the logical centers for focusing Federal support on health and other kinds of research. An early policy report stated, "(Universities) are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue truth wherever it may lead, there will be a flow of new scientific knowledge."[1]

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*After dinner address for Pfizer Postdoctoral Fellowship Awards Dinner, Four Seasons Hotel, Washington, DC, May 4, 1984.

**Director, National Institutes of Health, Bethesda, MD.

Industry's involvement with academia in research has traditionally been modest. Of all the funds going to academia for health R & D, industry's share is about three percent as compared with 77 percent from the Federal Government. It is just recently, since about 1978, that industry has become a strong factor in the biomedical coalition. The current rise of special arrangements between academia and industry to advance research and development is not, however, a radical departure. The seemingly sudden appearance of new industry-academia relationships on the biomedical scene arises from the rapid accumulation of recent scientific discoveries with practical applications.

As we discuss the evolution of formal research partnerships involving academic institutions, industry, and the government, it is well to remember that informal networks of collaboration among scientists have always existed and with little regard for their individual organizational affiliations. The nature of this collaboration is revealed in the footnotes or texts of almost any review article on a scientific subject.

To illustrate my point, permit me to cite, as a random example, an article that appeared in the August 1983 edition of Scientific American.[2] In the article, Dr. Sidney Pestka reviewed the history of interferon. Some 40 scientists are mentioned in the text for their significant contributions related to interferon since its discovery in 1957. The scientists did the work for which they were cited at 25 different institutions, including six major American academic institutions, academic institutions in Canada, Sweden, Switzerland, France, and Belgium, two institutes of the National Institutes of Health, five major industrial or pharmaceutical companies, and research institutes in Japan, Finland, Great Britain, and the United States. Perhaps even more significant is the fact that, in many instances, pairs or groups of scientists collaborated across industrial/academic, government/-academic, and government/industrial organizational lines, as well as across international boundaries.

A few statistics indicate the scope of collaboration in health research and development among government, academia, and industry--and the different "assignments" we each perform within that collaboration. Nearly 60 percent of all research funded by NIH is performed by universities.

Total national support for health R & D in 1982 was an estimated $9.2 billion. Of that total, 37 percent was supported by NIH, 37 percent by industry, and 26 percent by other Federal, state and local governments and private non-profit organizations. But when we look at all basic health research support, which totaled some $2.8 billion, 63 percent was provided by NIH and about 10 percent by industry.

Breaking down those figures further, by type of effort supported, we find these comparisons: NIH support in 1983 was allocated approximately 61 percent to basic research, 31 percent to research applications, and 8 percent to development. Our internal analysis of statistics from various sources found a different, but anticipated, trend in industry support: 10 percent for basic research, 45 percent for application, and 45 percent for development.

It is clear, then, that government and academia and industry perform complementary roles in the advancement and application of biomedical knowledge. One frequently describes this system of shared responsibilities as a "continuum" from basic research findings to application in medical practice. A more appropriate description would be a venn diagram with its intersecting circles, or a Rubik's cube with its three-dimentional alignments.

The new relationships in biomedical research forged between industry and academia recently have received a great deal of attention in science journals and business magazines. Even the world outside of biomedical science is aware of the multimillion dollar arrangements that have been formed in the last five years between major corporations and top academic institutions--especially in the area of biotechnology. This represents an increase in initiative by corporations in areas that just a few years ago had been considered the exclusive territory of the Federal Government. These arrangements, which in my opinion are better for their diversity, include corporations sending their staff members in increasing numbers back into academia for additional research training, and corporate support to universities to establish new facilities. Some companies are giving "seed" grants to young researchers with the hope that in the future they will be equipped to apply for Federal grants. Other universities have set up "consulting collectives" to link with industry in order to raise money to support the research of junior faculty.

NIH, too, has formed additional ties with the private sector. In 1981, under a departmental action, for-profit organizations were made eligible for grants from the Department and the NIH under a peer review mechanism similar to that used for academia-based scientists. Such firms have, of course, long been eligible for contracts with the NIH. Another industry-oriented initiative is the Small Business Innovation Act of 1982. Under the law, Federal agencies with R & D budgets exceeding $100 million are required to set aside a certain amount of their extramural R & D budgets for the SBIR program. The program, which is designed to stimulate technological innovation, uses small business to meet Federal R & D needs, and to increase private sector commercialization of innovations derived from Federal research and development. In FY 1983, NIH awarded 123 SBIR grants totaling $6.55 million.

The tantalizing opportunities promised by advances in basic research and the changing patterns of funding for biomedical research are the forces drawing the partners--industry/government/academia--together. We are faced with a richness of opportunity just at a time when leveling of Federal support of science seems to be a long-term reality.

The period of explosive growth of support for Federal support of biomedical research of the 50's and 60's is long over. After reaching a high in constant dollars in 1979, the NIH budget leveled off, and in the next three years declined about 12 percent in the same dollar. The increases of FY 83 and 84 have brought our budget almost back to the FY 79 peak in purchasing power, but the overall growth since 1970 has been only one percent per year. In the context of the present economy, NIH has been well treated by the Administration and the Congress, but we cannot anticipate extraordinary growth in the foreseeable future. In my view, we are facing more than

a temporary funding constraint in biomedical science; rather, we have entered a new, steady state that all of us--NIH, universities, and industry alike--would do well to view as the future norm.

The academic institutions, of course, are well aware of the shortfall in Federal funds and in recent years have awakened to the commercial value of some of their activities. As Barbara Culliton of Science magazine put it, "For the first time, in basic biomedical research, the university has something extremely valuable to sell."[3] That commodity is precious. It is excellence and creativity. The men and women working in science in the universities and medical schools expand the frontiers of science. Industry, on the other hand, is rarely able to analyze carefully the developing edges of biology in relationship to the industry's particular product lines.[4] Yet, industry is beginning to realize that in the long-term it would benefit from a more intensive involvement with academia.

Returns to the academic institution from relationships with industry include money for basic and applied research, access to certain technologies, access to special facilities, and the availability of staff exchange and consultations.

Industry is interested in forming ties to academia not altruistically to make up for the government's shortfall, but because it will help them succeed in their mission. Dr. Theodore Cooper, a former NIH institute director, former Assistant Secretary for Health, and currently with another pharmaceutical company, has called the reasons the five P's: patents--to gain patentable ideas or entities; patients--to have access to patients for clinical trials; publications--to have publications of clinical studies for use in securing FDA approval and as promotional aids; personnel--to attract scientists to the company as staff or consultants; and prestige--to have the prestige of association with academia's implied reliability and quality. All of these add up to the sixth "P"--profit.[5]

The Federal Government's justification for support of biomedical research has, over the years, emphasized quite properly the intangible and incalculable human benefits--the improvements in the quality of life--that have come from research. There can be no better reason for the current national investment.

But there is another effect of biomedical research. A five-year study attempting to quantify the worth of biomedical research was conducted in the late 1970's and its results were published in 1979 in a book by Selma Mushkin, titled: "Biomedical Research: Costs and Benefits."[6] The study addressed the question, "Is the public getting an appropriate return for the multi-million dollar yearly expenditure on health research?"

The answer is an emphatic "yes." For example, the returns to the gross national product from lives saved and work years of sickness averted exceed by a ratio of about 13-to-1 the total cumulative research and development costs for the 75-year period beginning in 1900. For the 45-year period beginning in 1930, the ratio was about 5-to-1. The more recent lower but still spectacular return reflects the high levels of basic, nonmission-oriented life science research of the past 40 years, whose payoffs will undoubtedly favorably affect future cost/benefit ratios.

But there remains a need to convince the public and its leaders that biomedical research is a blue chip national investment and the only hope for the United States to remain in the vanguard of the biological and technological revolution. If it is not enough that biomedical research provides payoff in terms of lives saved and work years preserved, then perhaps an argument regarding nonmedical translations of biomedical research would help. Industrial applications of the processes and incidental findings of biomedical research date back many years.

The NIH recently conducted a modest pilot study to identify discoveries in biomedical research that have been adopted by industry for commercial application outside the health care sector. They found interesting and, in some instances, surprising roots of ten well-established industrial processes or products. For example:

- Freeze drying was first developed in biomedical laboratories for preserving protein solutions without refrigeration. Subsequently, freeze drying has become a key process for food preservation.

- The development of flexible endoscopes, in part supported by NIH grants to the University of Michigan, was a critical event in fiber optic technology--now in a logarithmic growth phase with major applications in telecommunications, industrial process controls, and the military.

- The pilot study included the laboratory instrument computer called the Linc--a flexible and powerful scientific tool developed at M.I.T. under the direct sponsorship of the NIH in cooperation with NASA. The Linc not only had an impact on biomedical research but also on the desk top computer industry.

- Finally, enzyme biochemistry, a field that has received significant contributions from biomedicine, has been applied to the production of beer, leather, and laundry detergents. In the production of beer, enzymatic chillproofing has been adopted as a standard treatment to deter turbidity and sediment formation.

The 10 examples cited in the study were estimated to play a part in contributing about $37 billion annually to the gross national product--an amount that for comparison exceeds the total combined appropriations of the NIH since its inception, and is more than eight times our current annual appropriation.

In a recent article, George Keyworth, the President's Science Advisor, underlined a commitment by the Government to support basic research. He said, "Not only is basic research an essential investment in the nation's long term welfare, but it is largely a Federal responsibility because its benefits are so broadly distributed. Quite simply," he said, "basic research is a vital underpinning for our national well-being."[7]

In addition to its strong commitment to support basic research, NIH is also committed to the training and development of a cadre of able investigators. This new talent will be responsible for maintaining American technological and scientific leadership in coming years. Despite the fact that this is one of NIH's highest priorities, we are unable to do as much as we would like. This is why it is so crucial that industry contribute to the continuity and expansion of the investigator pool by increasing its support of training and career development in academic institutions. I would hope that other private sector organizations will prove as farsighted as Pfizer and set up programs similar to this fellowship program.

There are several other areas where the triumvirate can combine forces to deal with some of the important issues facing biomedical research today--for all three can benefit from their solution.

For example, because of common interests, increased participation with academia and government in clinical trials should be attractive to industry. There is an urgent need to secure additional support in order to aid the transfer of valuable scientific advances into medical practice. This is especially true for the development and testing of "orphan drugs." I am very pleased, in this regard, that the National Eye Institute and Pfizer are beginning a joint study of aldose reductase inhibitors for prevention of diabetic retinopathy and neuropathy.

Some very creative cooperative efforts at public education have also been undertaken by NIH and industry. For example, this past winter, Pfizer and the National Institute on Aging cooperated in a program to bring health promotion/disease prevention materials to the elderly across the country through programs at shopping malls.

Another matter requiring attention from the entire research community is the need to replace or purchase the increasingly sophisticated instruments required for today's research. In addition, laboratories and facilities are slowly deteriorating and need remodeling or replacement. Another area that should concern all three partners in research is the erosion of public support for use of animals in research. All of us need to do whatever is possible to build a public acceptance for careful, controlled and humane use of animals in research, lest our efforts to improve human health be irreparably stymied.

In summary, in an era of such great scientific opportunity, there is more than enough room for all three members of the government/industry/-academia triangle to engage their full resources and energies. Moreover, this new era of cooperation has just begun.

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INHERITED DISORDERS OF PURINE METABOLISM*

by

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Seven well-established inborn errors of purine metabolism are summarized in Table 1 according to the major manifestations of each enzyme abnormality. These are hypoxanthine phosphoribosyl-transferase deficiency, phosphoribosylpyrophosphate synthetase superactivity, xanthine oxidase deficiency, adenine phosphoribosyltransferase deficiency, myoadenylate deaminase deficiency, and adenosine deaminase and purine nucleoside phosphorylase deficiencies. An additional disorder, glucose 6-phosphatase deficiency, is included even though glucose 6-P'tase is not a purine enzyme, because its deficiency results in a marked secondary derangement of purine metabolism. Each of these conditions will be summarized briefly.

Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT) Deficiency.[1] The discovery of a virtually complete deficiency of hypoxanthine and guanine phosphoribosyltransferase activities in the erythrocytes of patients with the Lesch-Nyhan syndrome by Seegmiller et al. in 1964[2] ushered in what Lesch[3] has called "the purine revolution." The Lesch-Nyhan syndrome is characterized by chorioathetosis, spasticity, mental retardation, severe self-mutilation, and marked hyperuricemia and hyperuricaciduria.

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Renal stones and renal failure are common and gouty attacks may occur. The condition is X-linked and involves only male children. Life expectancy is markedly shortened but some patients have lived into their twenties with allopurinol and supportive therapy.

The consequences of HPRT deficiency will become clear from a brief review of normal purine synthesis and catabolism (Fig 1). The first specific reaction of purine biosynthesis involves an interaction of glutamine and phosphoribosylpyrophosphate (PP-ribose-P) to form phosphoribosylamine. This compound then undergoes several sequential reactions that eventually result in the formation of inosine monophosphate (IMP), the first complete purine compound. IMP may be converted to adenosine monophosphate (AMP) or guanosine monophosphate (GMP) which are precursors of coenzymes and of nucleic acids. They are also regulators of activity of the first enzyme of the pathway (amidophosphoribosyltransferase) as endproduct or feedback inhibitors of purine biosynthesis. AMP and GMP may also be broken down to ribonucleoside compounds and eventually to free bases hypoxanthine and guanine which are more direct precursors of uric acid. But not all of hypoxanthine and guanine is lost as uric acid; these bases are normally extensively reclaimed and reconverted to nucleotide stages by couplings with PP-ribose-P. In man, the reactions of PP-ribose-P with hypoxanthine and guanine are catalyzed by a single enzyme, hypoxanthine-guanine phosphoribosyltransferase, usually called simply HPRT. A similar salvage reaction with adenine is catalyzed by a different enzyme.

HPRT deficiency leads to a block in the salvage of hypoxanthine and guanine and also to accumulation of the PP-ribose-P not used in the absent phosphoribosyltransferase reaction. Hypoxanthine and guanine are quantitatively converted to uric acid, and in addition the excess levels of PP-ribose-P lead to increased rates of purine biosynthesis de novo and further loss of purine bases. The result is marked hyperuricemia and hyperuricaciduria.

In most patients with the Lesch-Nyhan syndrome, the residual amounts of HPRT are too low to be detected by immunological means and the enzyme may be absent altogether. However, in other instances the deficiency is attributable to molecular changes that result in altered affinities of the enzyme for a substrate or in altered catalytic reaction rates. In these instances immunological cross-reactive material is found, and in some cases an approximately normal amount of enzyme protein is present, though non-functional under physiological conditions.

When the genetic alteration of the enzyme allows some residual HPRT activity under physiological conditions, the severe manifestations of the Lesch-Nyhan syndrome do not appear and a syndrome known as "partial HPRT deficiency" results. This syndrome has as its chief manifestation marked hyperuricemia and gout or kidney stones at a relatively young age, and may occasionally be accompanied by a neurological disorder resembling spinocerebellar ataxia, but mental deficiency and compulsive self-injury are absent. Since the HPRT gene is X-linked, this disorder is also restricted to males, but some female

heterozygotes do show HPRT values intermedate between those of normal and affected subjects, and may have hyperuricemia or hyperuricaciduria, and may develop gout in later life. HPRT values in males with the partial HPRT deficiency syndrome range from 0.2 to 30 percent of normal. Partial HPRT deficiency appears to account for about 0.5 percent of adult gout.

Human HPRT is a tetramer comprised of four identical subunits of 217 amino acids in length, with a subunit molecular weight of 24,470. The structural gene for HPRT has an estimated length of 34 kb, whereas the mature mRNA is about 1.6 kb in length. The discrepancy is accounted for by the presence of eight introns in the functional gene.[4]

Structural and functional abnormalities have been defined for five mutant forms of human HPRT. One of these mutant enzymes came from a patient with the Lesch-Nyhan syndrome (HPRT-Kinston), the other four from patients with partial HPRT deficiency and gout or nephrolithiasis (HPRT-Toronto, -London, -Ann Arbor, and -Munich). These abnormalities are summarized in Table 2.[4]

Full length cDNA clones of the human HPRT have been prepared and transferred into HPRT-deficient fibroblast and D-98 Hela ($HPRT^-$) cells, with correction of the enzyme deficiency [5,6]. In addition, enzyme deficient human lymphoblasts prepared from Lesch-Nyhan patients have been partially corrected metabolically by use of human HPRT with DNA transferred by a transmissible murine retroviral vector [7], and transgenic mice have been produced with full-length human HPRT cDNA in minigenes constructed

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with various recombinant expression vectors.[6] The Lesch-Nyhan syndrome may be one of the first candidates for gene transfer correction studies in the human.

PP-ribose-P Synthetase Superactivity.[8] Screening of gouty patients with marked hyperuricemia and hyperuricaciduria disclosed some who had normal HPRT activity. Sperling[9] found one such subject who also had elevated erythrocyte levels of PP-ribose-P, and correctly surmised a primary increase in its rate of synthesis. He showed that PP-ribose-P synthetase was superactive at low phosphate levels compared with the enzyme from normal subjects. PP-ribose-P synthetase catalyzes the reaction of ribose 5-phosphate and ATP to form PP-ribose-P. The enzyme requires inorganic phosphate as an obligatory allosteric activator, and is normally inhibited by ADP (which competes with ATP) and by purine nucleotides in general (metabolic pool inhibition). The mutant enzyme discovered by Sperling had reduced affinities for nucleotide regulators in general and presumably was overactive under physiologic conditions. This resulted in excess synthesis of PP-ribose-P and continuous stimulation of synthesis of phosphoribosylamine, purine ribonucleotides and uric acid. Severe gout or kidney stones occur at an early age. The gene for PP-ribose-P synthetase is also X-linked, and the patients are males except that one female heterozygote is also known to be affected.

Although the total number of families known to have superactive variants of PP-ribose-P synthetase is small, at least four sub-types of this condition are known (Table 3). In addition to Type I (described by Sperling), Becker and colleagues have

reported patients with increased enzyme activity per molecule (Type II), with enzyme showing increased affinity for its substrate ribose 5-phosphate (Type III) or with a combination of Types I and II (Type IV).

Xanthine Oxidase Deficiency.[10] In this condition there is a block in the reaction that normally oxidizes hypoxanthine to xanthine and xanthine to uric acid. Usually the block is virtually complete but some patients appear to have a few percent of residual activity. Studies are limited by the distribution of the enzyme activity which is restricted to liver and small intestinal and rectal mucosa and colostrum or breast milk in the human. About 50 cases are known, many coming from the Mediterranean basin, especially from Lebanon and Spain. In this condition xanthine and hypoxanthine replace uric acid as the end products of purine metabolism. Urinary xanthine levels may be high enough to lead to xanthine stone formation. Some patients have developed a late-onset type of myopathy associated with xanthine crystals in muscle and a few have had episodes of acute arthritis suggested to be "xanthine gout," but this is not proven. About half of all known patients were asymptomatic, having been diagnosed following detection of a serum urate level of under 1.0 mg/dl.

A new condition has been recognized in an infant with combined xanthine oxidase and sulfite oxidase deficiencies due to an absence of a common cofactor containing molybdenum. The defect appears to involve an inability to synthesize the pteridyl moiety of the cofactor. Clinically, there was severe neurological dysfunction.

Adenine Phosphoribosyltransferase (APRT) Deficiency.[11] APRT normally catalyzes a salvage reaction in which adenine condenses with PP-ribose-P to form AMP. In subjects with APRT deficiency, adenine accumulates and is oxidized via the 8-hydroxy intermediate to 2,8-dihydroxyadenine (2,8-DHA) which is excreted in excessive amounts. 2,8-DHA is highly insoluble and may form renal stones. In APRT deficiency adenine metabolites may amount to 20-30 percent of the total purine excretion even on a low purine diet. The source of the endogenous adenine is probably the polyamine pathway of which adenine is a metabolic by-product; phosphorolysis of adenosine is probably only a minor contributor. The gene coding for human APRT is located on the long arm of chromosome 16. Heterozygote frequency has been estimated at 0.4 to 1.1 percent in several population studies. This suggests that homozygosity may be more frequent than presently recognized. At least 18 instances of homozygous APRT deficiency have been reported since the disorder was identified in 1974, most of them in Japan. Five of the 18 have been adults. Several patients had earlier been thought to have uric acid stones, as 2,8-DHA has spectral and chemical properties rather like those of uric acid, but the compounds can be distinguished by ultraviolet, infrared and mass spectrometry. Treatment consists of a low purine diet and allopurinol.

Myoadenylate Deaminase Deficiency.[12] In 1978 Fishbein et al.[13] described five patients with a history of skeletal muscle dysfunction following exercise in whom adenylate deaminase activity was virtually absent from muscle. Over 20 additional

patients have now been described. During normal exercise ATP is dephosphorylated and the product AMP is deaminated with release of NH_3. IMP accumulates in muscle and is reconverted to AMP in the purine nucleotide cycle, the enzymes of which are particularly active in skeletal muscle. In myoadenylate deaminase deficiency, exercise does not release NH_3 into the blood stream; this provides the basis for a presumptive diagnostic test. AMP rather than IMP accumulates with exercise, and is subject to nucleotidase action; adenosine, inosine and hypoxanthine are formed and are lost from the muscle. The concentration of total adenyl nucleotides falls markedly and remains depressed for hours.[14] Since ATP is the only source of energy for muscle contraction, these observations may account for the post-exercise symptoms in these patients. The types of muscle dysfunction, and age of onset, have shown wide variation. The condition is probably not rare: about 2 percent of muscle biopsy specimens accumulated in three centers for study of muscle disease showed myoadenylate deaminase deficiency. The condition shows autosomal recessive inheritance.

Adenosine Deaminase (ADA) and Purine Nucleoside Phosphorylase (PNP) Deficiencies.[15] Inherited deficiency of either ADA or PNP causes abnormalities of purine nucleoside metabolism that are selectively toxic to lymphocytes and results in severe immune deficiency disease in the neonatal period. Most patients with ADA deficiency lack both cell-mediated (T-cell) and humoral (B-cell) immunity and have severe combined immunodeficiency disease (SCID). Approximately 50 cases of ADA

deficiency have been detected; about 30 percent of known cases of SCID are due to ADA deficiency. PNP-deficient children have a severe defect of cell-mediated immunity but humoral immunity is relatively normal. Nine cases of PNP deficiency have been reported. Both conditions are inherited in an autosomal recessive manner. In ADA deficiency, adenosine and deoxyadenosine levels are elevated in plasma or urine, and dATP accumulates in erythrocytes and peripheral blood mononuclear cells. dATP is believed to accumulate preferentially in ADA-deficient T lymphocytes and to inhibit ribonucleotide reductase, thereby interfering with DNA synthesis. A second hypothetical mechanism invokes accumulation of S-adenosylhomocysteine secondary to adenosine increases, and inhibition of S-adenosyl-methionine-mediated transmethylation reactions vital to lymphocyte division and function. In PNP deficiency dGTP accumulates in T lymphocytes. The resultant inhibition of ribonucleotide reductase and DNA replication has been proposed as an explanation of the T-cell defect in PNP deficiency.

Glucose-6-Phosphatase (G6P'tase) Deficiency.[8] Patients with G6P'tase deficiency (von Gierke's disease) can metabolize exogenous or gluconeogenetic glucose to glycogen or lactate, but cannot release free glucose from glucose 6-phosphate in response to hypoglycemia. Glycogen breakdown in response to hypoglycemia consumes inorganic phosphate; the drop in intracellular phosphate is proposed to release adenylic deaminase from its normally inhibited state, with resultant loss of adenyl nucleotides and conversion of the purines to uric acid. The drop in

intracellular nucleotide levels is postulated to result in release of the first enzyme of purine biosynthesis (amidophosphoribosyltransferase) from inhibition, resulting in a compensatory increase in purine biosynthesis de novo. These postulates could explain both the hyperuricemia and hyperuricaciduria of von Gierke's disease and the evidence for increased purine biosynthesis de novo.

Hepatic Adenylic Acid Deaminase Variant in Primary Gout. Hers and Van den Berghe[16] have postulated a similar mechanism in primary gout associated with increased carbohydrate intake, except that they suggest the presence of an AMP-deaminase variant that is less than normally sensitive to phosphate or GTP inhibition. One deceased gouty patient has been described in whose liver appropriate studies of sensitivity of AMP-deaminase to phosphate and GTP inhibition supported this hypothesis.[17] This defect, if widely distributed in the populations, might explain some of what is now generally termed "idiopathic gout."

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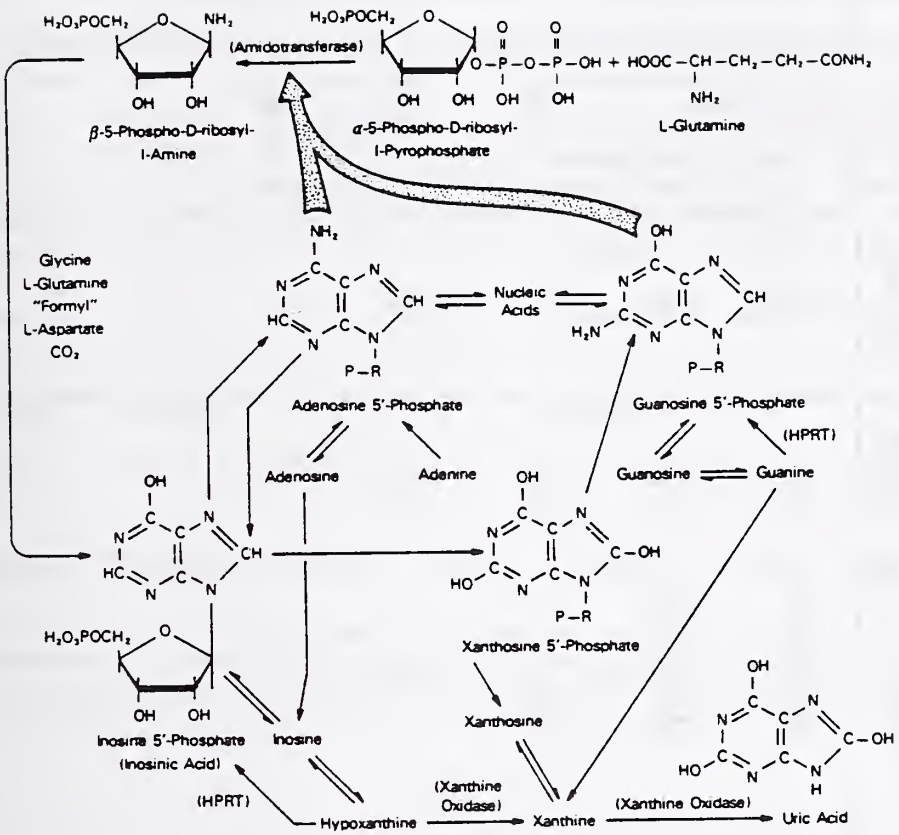
(Amidotransferase)
β-5-Phospho-D-ribosyl-
l-Amine
α-5-Phospho-D-ribosyl-
l-Pyrophosphate
L-Glutamine
Glycine
L-Glutamine
"Formyl"
L-Aspartate
CO2
Nucleic
Acids
Adenosine 5'-Phosphate
Guanosine 5'-Phosphate
(HPRT)
Adenosine
Adenine
Guanosine
Guanine
Xanthosine 5'-Phosphate
Xanthosine
Inosine 5'-Phosphate
(Inosinic Acid)
Inosine
(HPRT)
(Xanthine
Oxidase)
(Xanthine Oxidase)
Hypoxanthine
Xanthine
Uric Acid

FIGURE 1

INBORN ERRORS OF PURINE METABOLISM

Enzyme Deficiency	MANIFESTATIONS				
	Arthropathy	Renal Stone	Renal Failure	Myopathy	Immuno-deficiency
HGPRT	+ (Gout)	+	+		
PP-Ribose Synthetase ↑	+ (Gout)	+	+		
Xanthine Oxidase	+	+		+	
Adenine PPT		+	+		
Myoadenylate Deaminase				+	
Adenosine Deaminase					+
Purine N'Side Phosphorylase					+
Glucose G-P'tase	+ (Gout)	+	+	+	

TABLE 1

STRUCTURAL AND FUNCTIONAL ABNORMALITIES IN MUTANT FORMS OF HUMAN HPRT*

MUTANT ENZYME	CLINICAL PRESENTATION	MUTATION		FUNCTIONAL ABNORMALITIES			
		AMINO ACID SUBSTITUTION	POSITION	INTRACELLULAR CONCENTRATION	MAXIMAL VELOCITY	MICHAELIS CONSTANTS	
						HYPOXANTHINE	PP-RIBOSE-P
$HPRT_{Toronto}$	Gout	Arg → Gly	50	Decreased	Normal	Normal	Normal
$HPRT_{London}$	Gout	Ser → Leu	109	Decreased	Normal	Increased 5-fold	Normal
$HPRT_{Ann\ Arbor}$	Nephrolithiasis	N.D.	N.D.	Decreased	Normal	Normal	Normal
$HPRT_{Munich}$	Gout	Ser → Arg	103	Normal	Decreased 20-fold	Increased 100-fold	Normal
$HPRT_{Kinston}$	Lesch-Nyhan Syndrome	Asp → Asn	193	Normal	Normal	Increased 200-fold	Increased 200-fold

* PP-ribose-P denotes 5-phosphoribosyl-1-pyrophosphatase, Arg arginine, Gly glycine, Ser serine, Leu leucine, Asn asparagine, Asp aspartic acid. N.D. not determined, and the arrow "is replaced by." From: Wilson J.M., Young A.B., and Kelley W.M. New Eng J Med 309:900, 1984.

FIGURE 2

PP–RIBOSE–P SYNTHETASE VARIANTS

TYPE 1. REDUCED SENSITIVITY TO NUCLEOTIDE INHIBITORS

TYPE 2. INCREASED SPECIFIC ACTIVITY PER ENZYME MOLECULE

TYPE 3. INCREASED AFFINITY FOR RIBOSE-5-PHOSPHATE

TYPE 4. COMBINATION OF TYPES 1 AND 2

TABLE 3

"THE ROLE OF THE NIH IN IMPROVING PUBLIC HEALTH"*

by

JAMES B. WYNGAARDEN, M.D.**

It is an honor and personal pleasure to participate in this symposium celebrating the 50th anniversary of the Istituto Superiore di Sanita. On behalf of the National Institutes of Health of the United States of America, I salute you on this auspicious occasion! There are many close ties between the National Institutes of Health and the Italian scientific community, and especially this Institution. Professor Pocchiari is a frequent visitor to our offices and laboratories in Bethesda.

We have a large community of Italian scientists collaborating with American investigators in our intramural research programs at NIH. Currently, more than 150 scientists from Italy are working with our scientists in Bethesda. The Italian contingent of guest worker/scientists is the second largest group of foreign nationals participating in research at NIH.

Some of them have worked so long and closely with our researchers that we no longer consider them as guests. The distinguished Fogarty scholar, Gaetano Salvatore, has been collaborating with NIH scientists since 1960. Another visiting scientist that we consider one of us is Dr. Salvatore Aloj.

I should also mention that among the scientists who have taken part in our visiting program is Maurizio Pocchiari, son of our host, Professor Pocchiari. The young Dr. Pocchiari was a visiting fellow from October 1, 1980 to September 30, 1983, when he worked with one of our most distinguished scientists, Dr. Clarence Gibbs, Jr., in our Laboratory of Central Nervous System Studies.

As I have learned more about the Istituto, I have been impressed by the way in which your organization resembles the National Institutes of Health and also how it differs. I have been asked to talk about the NIH and how it fulfills its role in improving public health. I will emphasize some of the traditional concepts of public health, but in doing so, I wish to stress our belief that the most

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**Director, National Institutes of Health.

important contribution we can make to public health is through creative research investigation, carried out under the most rigorous standards of excellence.

In one of the administrative publications issued by the National Institutes of Health, the role of the agency is described in one sentence. The mission of the NIH, briefly stated, "is to uncover new knowledge that will lead to better health for everyone." This characterization correctly identifies research as the central concern of the NIH. It also strongly suggests that improvements in public health are dependent upon new findings from research.

As the principal biomedical research agency of the United States Government, the National Institutes of Health conducts or directly supports over 36 percent of all health-related research in our country. Last year, our one agency expended roughly the same amount for research as was spent by all of private industry in our country for biomedical research studies.

About 80 percent of the current NIH annual budget of $4.5 billion dollars is used for the support of research and research training in academic institutions, hospitals, and nongovernmental laboratories throughout the United States and worldwide.

A substantial amount of the funds awarded by the NIH to "outside" organizations is in the form of grants made in response to proposals initiated by individual scientists. In fact, more than one-half of our agency's total budget is allocated to the support of such investigator-initiated research projects. We believe that this nondirective approach to funding research is the most effective means for drawing out from our scientific community the most innovative and useful ideas. At the same time, since most of the research investigators we support are affiliated with universities or academic medical centers, an important dividend of the NIH program is to strengthen the academic environment. We refer to our relationship with academic institutions as a partnership. It is a mutually beneficial partnership that is an important resource for the academic institution and, furthermore, we consider the association to be essential to the NIH if we are to succeed in our mission to improve health by uncovering new knowledge.

More than one-half of the total budget of the U. S. Public Health Service is allocated to the National Institutes of Health, a fact that indicates the status accorded to research as an essential tool for the improvement of public health. In order to state more clearly what the NIH does, I will state what it does not do. The NIH is one of the five agencies of the United States Public Health Service. Each of the five has responsibility for a major aspect of the Federal Government's functions with respect to public health. For example, the activities of our sister agency, the Food and Drug Administration, are directed toward protecting the health of the Nation against impure and unsafe foods, drugs, and biological products, as well as cosmetics and other potential hazards. Another public health service component, the Centers for Disease Control, is the Federal agency charged with protecting the public health of the Nation by providing leadership and direction in the prevention and control of diseases and other preventable conditions. The CDC administers Federal quarantine activities and regulations, licenses clinical laboratories, and in carrying out its mission, maintains close working relationships with state and local health officials.

Another agency of the Public Health Service--the Health Resources and Services Administration--is concerned with health care resource problems, their distribution, quality, and cost effectiveness. The agency also is charged with providing leadership in the delivery of health services and has a variety of specific operational responsibilities as, for example, the Indian Health Service.

The PHS agency that most resembles the NIH is ADAMHA, the Alcohol, Drug Abuse, and Mental Health Administration. This agency, like NIH, conducts and supports research. It is also charged with providing leadership in the Federal effort to reduce and eliminate health problems caused by the abuse of alcohol and drugs and to improve the mental health of the United States generally. Unlike the NIH, however, ADAMHA is substantially involved in providing health care through regional and neighborhood clinics for subjects with alcohol or drug or mental health problems.

The operation of the NIH encompasses research in its broadest sense. It extends from the most basic of studies in the realm of molecular and cell biology to clinical trials of the safety and efficacy of new drugs and vaccines. The agency conducts research in its own laboratories, supports research in non-Federal laboratories, in universities, medical schools, hospitals and research institutions throughout the United

States and abroad (in more than 1,250 institutions); it also helps in training of research investigators; and fosters and supports biomedical communications.

Currently, about 62 percent of NIH's research budget is devoted to studies classed as basic or fundamental. At the same time, however, throughout the agency, there is a strong sense of the relevance of all research to public health. The name of our agency is in itself an expression of that policy. We are not the "National Institutes of Biological Research" or the "National Institutes of Biomedical Science" but the National Institutes of Health.

The NIH administers a comprehensive research program that seeks to understand the nature of disease. The product of this research is essential knowledge about life, disease, and malfunction. The ultimate aim is to prevent disease and premature death and to assure each person the maximum opportunity for a productive life free from disability.

Prevention and health promotion programs can only be as strong as the research base upon which they are founded. Therefore, it is particularly important to strengthen the scientific and technical base.

Each year, the NIH ascertains how much of its total budget is expended for prevention research. In the current year, our expenditures for activities defined as prevention research are in excess of one billion dollars. We define prevention research as that which is designed to yield results directly applicable to measures to prevent disease or the progression of presymptomatic disease. We also consider as prevention research those activities which have a high probability of yielding results that likely will be applicable to disease prevention or health promotion. Basic research efforts of this sort generate the fundamental knowledge that contributes to the development of future preventive interventions.

Such an effort by Dr. Robert Gallo and his associates at the National Cancer Institute recently yielded evidence that a variant of a human cancer virus called HTLV-III is the primary cause of acquired immune deficiency syndrome (AIDS). The scientists were able to isolate the HTLV-III viruses from 51 infected persons; to develop a method for growing the viruses in T-cells in the laboratory in bulk amounts; and to characterize biochemically and immunologically the proteins and genes of the viruses.

It is now predicted that it soon will be possible to have the amounts of viral protein needed for large-scale screening of blood samples by blood banks and diagnostic laboratories. Rapid tests for antibodies to HTLV-III in human blood are already feasible. Scientists also foresee the possibility of the development of new ideas for treatment and the possibility of a vaccine for AIDS.

The developments regarding AIDS provide an example of the immediate relationship that can exist between the most advanced research and the development of an important public health measure, in this case a large-scale method for screening as a means to prevent the transmission of AIDS through blood transfusions or blood products made from contaminated blood supplies.

Another recent development of consequence to public health was announced March 30 when the results of tests with an experimental flu vaccine were published in Lancet. The new vaccine which contains live virus is given as nose drops. Studies of the level of immunity established in human subjects suggests that the new vaccine developed through the National Institute of Allergy and Infectious Diseases will prevent the spread of the flu virus better than flu shots. Studies are now underway to determine how long the new vaccine is protective and to learn its safety and effectiveness for people at high risk of serious complications from influenza.

Research of another sort, clinical trials conducted or supported by the NIH, also plays a key role in making possible public health advances.

The National Heart, Lung, and Blood Institute recently concluded a multicenter, randomized clinical trial to determine the safety and effectiveness of administration prior to birth of a steroid drug, dexamethasone, in preventing infant respiratory distress syndrome (RDS), a risk for babies born prematurely before their lungs have sufficiently matured. In the study, mothers at high risk of premature delivery were administered the steroid 24 to 48 hours prior to delivery in an attempt to enhance lung maturation. At birth, premature female infants whose mothers received the drug, were four times less likely to develop RDS than those whose mothers were not. Male infants did not benefit from the treatment. The investigators reporting in the February 1984 issue of the Journal of Pediatrics concluded that careful use of the steroid can be expected to become a part of the management of high-risk deliveries.

The results of another clinical trial conducted by the National Heart, Lung, and Blood Institute were announced January 12. At that time, the findings of a major clinical trial showed for the first time that the reduction of elevated blood cholesterol results in a reduction in risk of heart attack. The ten-year trial was carried out in 12 clinical centers in the United States and Canada. A total of 3,806 men who were healthy except for elevated blood cholesterol concentrations were assigned randomly into two groups. Each group received instructions for a moderate cholesterol-reducing diet. One group was then administered a cholesterol-lowering drug; the other group received a placebo. Compared with the placebo group, the drug-treated group experienced a 24 percent reduction in fatal heart attacks and a 19 percent reduction in nonfatal heart attacks. The findings are expected to have a considerable impact on American medical practice.

I have given a few examples of the direct translation of research into applicable means for disease prevention. In recent years, the NIH has become involved in another type of public health activity--health promotion or health education programs. The outstanding example of such an effort at the NIH is the National High Blood Pressure Education Program.

An estimated 60 million Americans have high blood pressure that increases their risk of illness and premature death. Of these persons, 35 million need some form of continuing treatment--the remaining 25 million have borderline high blood pressure that requires medical surveillance. Untreated hypertension is the largest single contributor to stroke and a major contributor to heart disease and kidney failure.

The High Blood Pressure Education Program, started in 1972, has helped to improve hypertension control in the nation. With physicians and the public better informed about hypertension, patient visits and medication prescriptions for hypertension have increased as has the number of persons whose hypertension is well controlled. Associated deaths, especially from stroke, have declined rapidly and dramatically. Since the education program began, there has been a decrease in cardiovascular mortality in our country of over 40 percent. While a direct cause and effect relationship cannot be demonstrated, certainly it appears that this program has contributed substantially to gratifying progress in public health.

Another type of public education program was launched in March of this year by the National Cancer Institute. The program is a major federal effort to increase public awareness of

the possibililites for cancer prevention. It presents a challenge to the American people to learn what they can do everyday to control their own cancer risks. It is a kind of second generation awareness program, partly designed to counter the public confusion and pessimism generated by earlier warnings against various cancer causes. An opinion survey conducted last year by the Cancer Institute revealed that many people believe--quite erroneously--that "everything causes cancer," and that there is not much a person can do to prevent it.

The new program will be based on the most recent scientific information related to cancer cause and prevention and will offer specific tips for individual action.

The high blood pressure and the cancer awareness programs are relatively rare activities for the NIH. Most of our informational activities for the general public are not so highly structured and are mostly responsive in nature. Even so, the NIH provides a substantial amount of health-related information directly to the general public. Each year we receive from 400 thousand to half a million inquiries from members of the general public, either by mail or telephone.

The NIH takes seriously its obligation to provide requested information to members of the public, and a large part of its annual expenditure of $7 million for printing and distributing publications is allocated to materials for the public inquirer.

Over the past decade, the NIH has taken an increasingly active role in communicating the findings of research to the health professional community. Obviously, the output of biomedical research in terms of individual findings covers a very broad spectrum ranging from discoveries at the frontiers of biology to readily applicable means of disease prevention, diagnosis, or treatment. Each element in the array of findings is useful either to the research scientist or to the clinician or to both. However, the busy practitioner would not only be inundated by the sheer volume if the full output of published results were channeled to him or to her but certainly would not have time to identify these findings which might be applicable to practice. For this reason, it is essential that there be a sorting out process and that communications efforts be concentrated on the relatively small portion of current research output that is ready for use by the health professional in patient care. There are many channels of communications with the practitioner--some are highly structured--others are patterns of custom.

Academic health centers are key communicators. They take seriously their responsibility for the continuing education of their own graduates and, in many instances, for health professionals practicing in their geographic area. Specialty and professional organizations support many individual programs of continuing education as well.

The NIH now engages in the very considerable amount of direct communication with practicing health professionals. During the average year, it sponsors about 100 seminars and other meetings for practicing physicians which in the aggregate are attended by perhaps as many as 10,000 doctors. In a typical year, the NIH responds to more than 80,000 inquiries from physicians, either by mail or telephone, and prepares more than 170 different publications for the use of physicians. In addition, the NIH publishes some 135 different informational brochures for the physicians to use in patient education. Three-quarters of a million copies of such publications are distributed upon request to practitioners in a normal year.

The National Cancer Institute supports 20 comprehensive cancer centers scattered throughout the Nation which exert a significant impact through effective cancer control, demonstration and outreach programs. These centers are focal points for community efforts to assure widespread use of the best available methods for early detection and diagnosis of cancer and dissemination both at the lay and professional levels. The centers are designed to be places to which individuals and their physicians can turn for information, help and advice.

In addition, the multidisciplinary general clinical research centers supported by the NIH at 75 medical centers have served as demonstration and communication centers for more than two decades.

In 1978, the NIH Director created a new unit in the central administration charged with improving the transfer of research findings from the laboratory to their application in the diagnosis, prevention, or treatment of disease. In carrying out its charge, the newly established Office of Medical Applications of Research began by launching a novel activity called the consensus development conference.

The consensus development conference provides a neutral forum for a thorough public discussion of the scientific pros and cons of new modes of treatment or preventive measures, as well as of long-established practices about which doubt or question may have arisen. Over 40 such conferences have been

held. At each, a consensus panel of experts in the relevant disciplines, usually including lawyers, ethicists and others with direct interest in the problem under discussion, sit as a kind of jury. They hear statements from responsible spokespersons representing differing points of view on the subject under discussion. Usually the testimony lasts for two days, following which the panel attempts to develop a statement of consensus on the question under discussion.

The first consensus conference addressed a question that had been raised about the risks versus benefits of mass screening of all women for breast cancer, using X-ray. Did the benefits of such diagnostic screening outweigh the potential of adverse effects from ionizing radiation? In this instance, the consensus panel included not only leading oncologists and surgeons but also psychologists, attorneys, clergymen, and representatives of women's groups. The panel recommended that women under 50 not be subjected to X-ray screening in the absence of certain predisposing factors. Although the consensus statements have no effect as regulation, it is obvious that they would be regarded as important.

Recent conferences have covered such diverse subjects as "Dental Sealants in the Treatment of Tooth Decay"; "Hip Joint Replacement"; "The Use of Estrogen Therapy to Prevent or Retard Osteoporosis"; and "Uses of Ultrasound Imaging in Pregnancy."

Results of the consensus conferences are published in the Journal of the American Medical Association as well as other medical journals. Copies of the consensus statements are mailed promptly to some 22,000 physicians nationwide who have asked to be given such information. The primary purpose of the consensus conference is to aid in the transfer of research-derived information to the practicing health professional, but there has also been substantial public interest in this activity. It is not unusual to have 30 newspaper, magazine, and television reporters present at the announcement of the panel's consensus statement. At one recent conference, 60 reporters attended the briefing at the end of the conference.

Lastly, I will mention a highly important and unique component of the National Institutes of Health that constitutes a critical instrument for improving public health--the National Library of Medicine. The Library collects, organizes, and makes available biomedical information to investigators, educators and practitioners and carries out programs designed to strengthen medical library services in the United States and

in other countries. As the central resource of the existing national biomedical information system, it is an essential element in the public health establishment in our country.

The Library's comprehensive collections and information services at its main headquarters on the NIH campus in Bethesda are used extensively by health professionals and health science students. But more importantly, the NLM serves as a national resource for all U. S. health science libraries. Lending of books and other services are provided through a regional medical library network serving well over 2,000 hospital and medical school libraries.

The library's computer based Medical Literature and Analysis Retrieval System (MEDLARS) was established to permit health professionals throughout the Nation and in many parts of the world to achieve rapid access to NLM's vast store of biomedical information. The Istituto Superiore di Sanita is directly connected with the National Library of Medicine and acts as the hub for some 40 MEDLARS terminals serving the scientific community throughout Italy.

In closing, permit me to reemphasize my earlier statements about the dependence of successful public health programs upon the knowledge base that can be produced only through active research. As you begin the second half-century of the life of this important institution, I would urge that you continue to foster the spirit of inquiry and that the maximum feasible investment of human and other resources be devoted to the search for indispensable knowledge.

# # # #

OPENING REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

It is a pleasure for me, on behalf of NIH as well as for myself, to join in recognizing a great scientist and much beloved colleague, Julius Axelrod. During the next two days, all in attendance at this symposium will be treated to a full spectrum of information on the mechanisms of synaptic regulation. We are fortunate to be able to hear from the broad array of experts brought together for this program. Their presence here has special significance--for the distinguished scientists who will be telling us of their work have something special in common: each is a first or second generation disciple of Julius Axelrod.

While all of us subscribe to the belief that one person can make a difference, seldom are we privileged to see so graphic an example of this axiom as this symposium presents. In this conference, the presenters as well as the presentations constitute an impressive demonstration of the direct and personal influence of one individual--Julie. I fell under that influence a long time ago. In my first incarnation at NIH in 1953, I shared a carpool with Julie. Other members were Gordon Tomkins, Marvin Siperstein, and Jud Van Wyk. For thirty minutes twice a day, we were privileged to share the benefits of Julie's restless and incessant curiosity. For a year, Julie and I worked in adjacent laboratories in Building 3 in Steve Brodie's group. I have never seen any scientist work more efficiently and with less wasted motion than Julie. At that time, none of us had an office. But Julie, I'm happy to read in Science magazine that at long last Fred Goodwin has given you one.

Among Julie's many honors and accomplishments, I am sure that none has more meaning for him than the cadre of investigators of whom the speakers at this symposium are representative. What is essentially the "Who's Who in Neuropharmacology" is made up of those investigators who were enticed into this field by the personality and work of Dr. Axelrod. Many of them were nurtured by him into scientific maturity.

In other forums, Dr. Axelrod's scientific accomplishments have received worldwide acclaim. In this one, recognition is being given not only to his achievements in research but implicitly to his unusual

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*Symposium "Mechanisms of Synaptic Regulation" in recognition of Dr. Julius Axelrod, National Institute of Mental Health, held at the National Institutes of Health, Bethesda, Maryland, May 31, 1984.

**Director, National Institutes of Health.

ability as a teacher. While Julie exhibits none of the flamboyance that might be expected of one who has accomplished as much as he has, his modest intensity provides a perfect illustration of what Alfred Whitehead has described as one of the essential functions of a teacher; that is, "the ability to elicit enthusiasm by resonance from his own personality."[1]

This occasion is an expression of one of the highly important characteristics of the intramural scientific activities on this campus--their function as effective training programs. We often speak of the ways in which this Institution resembles a university, but this symposium illustrates that the similarity is deep and pervasive. In many parts of the world, "alumni" of the NIH intramural program occupy positions of leadership--deans, department chairmen, top officials in pharmaceutical firms, research foundation heads, productive scientists. For what it is worth, I will note that three Directors of NIH were at one time junior scientists in the intramural programs here.

This symposium is expressive of another essential feature of our intramural programs--the integration of scientific effort in a variety of disciplines. There is little if any concern about organizational lines. The juxtaposition of personnel from different disciplines and different institutes is recognized as a source of strength rather than of picayune concerns about turf. From such diversity, collaborative efforts are certain to be enhanced.

The working relationships that exist between the National Institute of Mental Health and its counterparts within the National Institutes of Health are remarkably close. In his forthcoming book on intramural NIH, DeWitt Stetten refers to these relationships as "matrimonial entanglements." Whatever the legal status, the productivity and harmony of this collaboration can largely be attributed to the constructive attitudes and sensitivity of colleagues like Julius Axelrod and Fred Goodwin.

On behalf of the NIH part of this team, I express to them our appreciation and extend to the symposium participants and members of this audience the warmest welcome.

Julie, we salute you.

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[1]Alfred North Whitehead, The Aims of Education, The New American Library, New York, 1955, p. 51.

OPENING REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

Without in any way detracting from the deserved recognition being given our honorees today, it is only fair to say that they are representative of hundreds of others. For the NIH is truly a remarkable place. I am aware that I could be accused of chauvinism in making such a statement, but as I have become better acquainted with the people of NIH, I have become more than ever convinced that here indeed is a special community. I say this because in spite of the extreme diversity of the demands on our personnel, the NIH as an organization is successful--it works.

Although our mission as an Agency is scientific in nature, it is not just technical competence that is needed to make the NIH work. John Gardner's comments about the Nation as a whole are on target for the people of NIH. He said, "A society such as ours is dependent upon many kinds of achievement, many kinds of complex understanding. It requires large numbers of individuals with depth of judgment, perspective, and a broad comprehension of the problems facing our world."

We honor such people today.

Even a cursory glance at the citations accompanying today's awards gives a sense of the range and scope of the activities taking place here. At least a score of distinct occupational categories are represented by the awardees. Among them, laboratory scientists, clinical specialists, technical information specialists, health science administrators, a landscape architect, a maintenance engineer, a secretary, personnel administrators, and so forth, to name a few.

From the written nominations and from what I have been told or know about the awardees, I am convinced that there is an arresting story of accomplishment back of each award.

In today's ceremonies, it will be my privilege to present the NIH Director's Award, the PHS Commendation Medal for Commissioned Officers, and two special awards for Equal Opportunity Achievement.

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*Fourteenth NIH Awards Ceremony, National Institutes of Health, Bethesda, Maryland, June 4, 1984.

**Director, National Institutes of Health.

One of the latter category--the Harvey J. Bullock Jr. Award for Equal Opportunity Achievement--is made in recognition of the late Mr. Bullock's efforts and achievements in this area. It is given to recognize significant individual efforts in furthering equal opportunity by persons who are not EEO program leaders.

The NIH Equal Employment Opportunity Award of the year is given to the person selected NIH wide from those who have received cash awards during the year from within the Bureau, Institute, or Division where they are employed.

I will have the pleasure of presenting the Commendation Medal to members of the Commissioned Corps of the Public Health Service. This award recognizes sustained high quality work performance in scientific, administrative, and other professional fields, the application of unique creativity to important problems, and significant professional contributions. Award of the Commendation Medal recognizes a high level of proficiency and special dedication.

The NIH Director's Award is relatively new, but as was intended by its originator, Dr. Donald S. Fredrickson, it has come to have special meaning. The award is designed to recognize exceptional performance by personnel in the Civil Service as well as in the Commissioned Corps. It is for persons who have made substantial or exceptional contributions to the benefit of the programs or the people of the NIH. By definition, the awardee's work performance must be clearly outstanding and directly related to fulfilling the NIH mission.

As an aside, let me note that the choices among the many nominees for these awards are not easy ones. In evaluating the nominations, careful attention is given to such points as the extent to which the field of health or biomedical research has been strengthened or improved by the individual's particular superior service or achievement. Another criterion is the extent to which the applied ideas, concepts, etc., represent originality, creativeness, or initiative. A point of special interest is the extent to which unusual ability has been exercised in solving difficult problems or the extent to which competence or resourcefulness improved the scientific or administrative management of the NIH. Some will receive the Director's Award in recognition of a high degree of demonstrated skill and leadership in administration or science.

I feel sure that as you hear the citations read, you will share my feeling of pride in being associated with the people of the NIH.

It is not surprising that the morale among members of the NIH community is high. It is not the result of some massive "be kind to employees" campaign on the part of the Agency's administration--rather it comes from within the individuals who carry out the unbelievably complex and varied range of activities required by our programs. It is generated within by the knowledge that we are doing something tremendously worthwhile and doing it well.

Perhaps the secret is in a bit of wisdom expressed by John Mason Brown: "Existence is a strange bargain," he said. "Life owes us little; we owe it everything. The only true happiness comes from squandering ourselves for a purpose."

# # # #

EXCELLENCE & CREATIVITY*

by

JAMES B. WYNGAARDEN, M.D.**

President Ruppert, Dean Kemph, members of the Board of Trustees, members of the faculty, graduates and friends --

I would like to begin by bringing you greetings from your sister city of Toledo, Spain, which I visited three weeks ago in connection with an official visit to that country. That, too, is a great city, a center of excellence and creativity. I have long greatly admired El Greco, and was particularly impressed with his paintings of St. Sebastian, tied to a stake, his body punctured with arrows. As Director of the National Institutes of Health, I thought those pictures could have represented almost any public official in Washington.

Incidentally, my guide pointed out that even though Toledo is the home of the Cardinal and the Cathedral is considered the first Church of Spain, the term "Holy Toledo" refers not to the city in Spain but to this city in Ohio.

For those of us who have spent a substantial number of years as medical school faculty members, three seasons of the year come to have special meaning for reasons other than meteorological. The highlight of the fall is the opening of the school year; for the faculty of the clinical departments, midsummer means the initiation of new housestaff; and, for everyone, late spring means commencement. Of the three events--commencement is by far the least threatening--the most laid back. I am delighted to have this opportunity to celebrate with all of you the success this occasion represents for the Class of 1984 of the Medical College of Ohio at Toledo.

It is customary for commencement speakers to dwell upon the challenge of the future to such a degree as to downplay the significance of the achievements being recognized by these exercises. I am aware that it has not been easy for you to get to this point, and I extend to you my heartiest congratulations. Each of you has excelled, and the degrees being conferred on you are badges of excellence.

In this context, I will express a few thoughts on the quality of excellence and on its logical product--creativity.

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*Commencement Address, Medical College of Ohio, Toledo, June 8, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

The word "excellence" implies competition. Strictly speaking, it is not possible to describe excellence in a vacuum. If we say that something or someone is excellent, the statement has little meaning unless we can supply the context--"compared with what?" For the individual, we usually make the obvious comparison--that is, competition with others--as our standard of excellence.

We often allude to universities or research institutions as "centers of excellence." In doing so, we are describing more than a magnificent facility populated by a community of distinguished scientists and educators. The excellence in such centers is much more likely to be the result of a constant interaction that draws out from students, scientists, and faculty alike the extra effort and dedication that would not be demanded in a less competitive setting. This, by the way, is why such great care is exercised in selecting students for admission to medical or graduate school. The quality of a school is to a very great extent determined by the quality of the students it accepts. Interactions among students are such that an outstanding freshman class tends to be an outstanding graduating class--and, in addition, it will have a stimulating influence on all its contemporaries for its four-year life.

Lewis Thomas, in looking back on his own experience as a medical student, attributed much of his education to his fellow students. In his book on "The Youngest Science," Dr. Thomas remarked, "When I am asked . . . which member of the Harvard faculty had the greatest influence on my education in medicine, I no longer grope for a name on that distinguished roster. What I remember now, from this distance, is the influence of my classmates. We taught each other; we may even have set careers for each other, without realizing at the time that so fundamental an educational process was even going on."[1]

But to return to excellence and the Class of 1984.

I need not tell you that your admission to medical or graduate school was competitive--requiring a high degree of demonstrated excellence. Such excellence was judged in large measure by your success in coping with baccalaureate academic requirements. More than most, medical and graduate students can appreciate the aptness of the word "curriculum." The word conveys the image of a racetrack, through its Latin root--the verb meaning "to run."

During your sprints in running the race courses--the curricula required for graduation--you were constantly reminded by your coaches, as well as by your competitors, of the pace required of those who would excel. But as you progress in your postdoctoral training, you will become more of a lonely long-distance runner and you will set your own pace. You will no longer be running in competition with others as much as you will be competing against your own standards; running to reach your own potential.

As we advance in training and experience, this set of self-generated standards comes into play for each of us. For it is then that our personal definition of excellence and our responses to it determine the level of our competence to fulfill the high promise with which our careers of service were begun. The answer to the question "compared with what?" ultimately becomes an expression of our personal goals.

What is the source of these internal standards? I personally believe that excellence genes are far more widely distributed in the population than is generally realized. One of the functions of education is to make it possible for individuals to achieve in ways they thought were beyond their capabilities. This takes place largely through the generation and nurture of an appreciation of excellence.

In his essays on "The Aims of Education," Alfred North Whitehead used the term "culture" in discussing the development of the consciousness of quality, which is the essential element of any personal standard of excellence--whether for doctor, lawyer, teacher or priest.

"Culture," he said, "is activity of thought and receptiveness to beauty and humane feeling. Scraps of information have nothing to do with it. A merely well-informed man (or woman) is the most useless bore on God's earth. What we should aim at producing is men (and women) who possess both culture and expert knowledge in some direction. Their expert knowledge will give them the ground to start from and their culture will lead them as deep as philosophy and as high as art. We have to remember that the valuable intellectual development is self-development."[2]

In 1978, the Presidents of 15 leading American universities jointly authored a report called "Research Universities and the National Interest." In the report, the Presidents made a general statement which, without mentioning the word, is a commentary on excellence.

"First-rate work in any field of human action is rare and difficult," they said, "but nowhere is the quality of work more decisive than in higher learning and research. It is hard to tell in advance who will do first-class scholarly and scientific work. Sometimes such work is recognized only slowly. Moreover, when a problem is extraordinarily resistant, even first-class work can fail. But none of these qualifications detracts from the force of the proposition that it is quality that counts. In the simple words of (the late) Philip Handler, 'In science, the best is vastly more important that the next best.'"[3] The same could surely be said of the practice of medicine.

In discussing excellence, we should not overlook its relationship to the passage of time. For excellence is an ephemeral term. What is excellent today may tomorrow be mediocre. So the person who would be excellent must be currently informed--that is to say--sustained excellence is utterly dependent upon continued learning.

John Gardner remarked that "Commencement speakers are fond of saying that education is a lifelong process. And yet," he added, "that is something that no young person with a grain of sense needs to be told." He then asked, "Why do speakers go on saying it?" And supplied an answer. "It isn't that they underestimate their audience. The truth is that they know something their young listeners do not know--something that can never be fully communicated.

"No matter how firm an intellectual grasp the young person may have on the idea that education is a lifelong process, he can never know it with the poignancy, with the deeply etched clarity, with the overtones of satisfaction and regret that an older person knows it. The young person has not yet made enough mistakes that cannot be repaired. He has not yet passed enough forks in the road that cannot be retraced."

Then Gardner added that "The commencement speaker may give in to the temptation to make it sound as though the learning experiences of the older generation were all deliberate and a triumph of character--character that the younger generation somehow lacks. It is not easy," Gardner says, "to tell young people how unpurposefully we learn, how life tosses us head-over-heels into our most vivid learning experiences, how intensely we resist many of the increments in our own growth."[4]

Gardner was saying that we may learn the most when we encounter problems we don't know how to handle and from which we can't retreat--an apt description of what you are likely to encounter often as a resident physician and throughout your professional life. Such unanticipated circumstances can severely test your personal concept of excellence and challenge your commitment to high standards.

Sheer talent does not equate to excellence. Keeping fully informed is essential but does not guarantee maintenance of excellence. Unless it is put to risk in performance, excellence soon fades. It is ultimately the quality of performance that counts.

The term "creativity" almost inevitably comes to mind when thinking about excellence. It might roughly be defined as "dynamic" excellence.

Creativity takes many forms. Wherever it is applied--in the practice of medicine--in research--in teaching--in administration--it carries with it the qualities of excellence, the spirit of inquiry and the application of curiosity and imagination.

Imagination is a kind of latent creativity. It is natural for young people to be imaginative and if this imagination can be coupled with discipline, its energy can be a lifelong strength. Whitehead remarked that a "tragedy of the world is that those who are imaginative have but slight experience and those who are experienced have feeble imagination." And that "fools act on imagination without knowledge, pedants act on knowledge without imagination."[5]

It is not easy to describe the process of creativity. Sir William Osler had his explanation for creative progress in medicine. He said, "A master word . . . is directly responsible for all advances in medicine over the past 25 centuries . . . the master word is 'work.'"[6]

But in Sir Alexander Fleming's account of the discovery of penicillin, a dramatically different quality of creativity is suggested; namely, the role of chance. He said, "There are thousands of different molds and there are thousands of different bacteria and that chance put that mold in the right spot at the right time was like winning the Irish Sweepstakes."[7]

The great French scientist, Claude Bernard, echoed Fleming's comment about the accidental nature of creativity but added another important dimension to the thought. Bernard said that "Experimental ideas are very often born by chance as the result of fortuitous observations . . . we walk, so to speak, in the realm of science and we pursue what happens to present itself accidentally to our eyes."[8] The same idea was economically expressed by Franklin P. Adams when he said, "I find that a great part of the information I have was acquired by looking up something and finding something else on the way."[9] Perhaps it is useful to emphasize that both Bernard and Adams linked creativity to activity. Serendipity is a dividend of action.

Any discussion of the role of chance as it relates to creativity in science is incomplete without the moderating words of Louis Pasteur, "Chance favors only the prepared mind."[10] Even before Pasteur, Joseph Henry, the American physicist, had noted that "The seeds of great discoveries are constantly floating around us, but they only take root in minds well prepared to receive them."[11]

The variety and power of preventive and therapeutic measures that we take for granted in 1984 would have seemed miraculous in 1934. Recall that sulfanilamide was discovered to have therapeutic value only in 1935. But medical historians correctly remind us that the useful application of the miracle drugs was possible only because the necessary preparatory work had been done. For example, before penicillin could be identified as a powerful means for preventing rheumatic fever, it was necessary to have perceived the connection between the disease and streptococcal infection. The supremely valuable uses to which the chance discovery of

penicillin was put depended in most cases upon preparation through decades of labor in the infectious disease laboratories; once again validating Pasteur's observation about preparation for chance.

There is creativity in the long hard pull of meticulous observation as well as in the flash of insight. There is creativity in the practice of medicine as well as in the conduct of basic research. In their essay, "On Blind Men, Elephants, and Floppy-Eared Rabbits," science historians Judith Swazey and Karen Reeds wrote "Many paths of inquiry and discovery about life processes have begun through efforts to understand and to intervene in states of disease." They commented that this fact has received little more than anecdotal mention in the literature on the nature and history of scientific research. Instead, in many instances, they said, there is a "stereotyped view of how research and discovery proceed . . . by some sort of necessary progression from disinterested 'pure research' to the application of the basic knowledge thereby gained for the solution of 'practical problems.' Such a progression, however, is neither necessary nor logical, but instead, only one possible path to scientific discovery, new knowledge, or the solution of practical problems."[12]

The well-trained physician has valuable and unique insights to offer across the entire spectrum of biomedical research. It is for this reason that the National Institutes of Health has developed special research training programs for physicians. There simply isn't enough time in the medical school curriculum to give the kind of research training that is essential for those who would devote themselves to investigative work at the complex frontiers of today's medical science.

Notwithstanding the spectacular progress that has been made, medicine today still calls for better than our best. The major health care problem of our time lies in the continued existence of diseases for which we can do little. Even if the best of contemporary medicine were universally available without financial barriers, cancer would continue to kill, rheumatoid arthritis would continue to cripple, and schizophrenia would continue to render insane. Medicine as a science is far from complete. It will remain so for science itself is by its nature incomplete. But science is not static. Medical science constantly moves forward--its motion fueled by the fresh insights of research investigators and alert practitioners.

The Hippocratic oath fails to mention two particularly pressing responsibilities of today's practitioner--the obligation not only to stay abreast of the state of knowledge in his or her area of medical practice, but also to assist in adding to that store of knowledge.

Whatever the career plans of the individual members of the Class of 1984, opportunities will present themselves for each of you to further medical science.

Cooperative arrangements have been worked out in various areas of medical research--for example, cancer--whereby the individual community practitioner becomes an important participant in major clinical trials. Such involvement can prove to be a major benefit in multiple ways. It puts the physician in direct contact with advances in the field under study--it provides patients with treatment derived from the findings of the newest clinical research and, finally, nationwide studies can be enhanced through increased numbers of subjects and enriched by vital input from physicians who serve at the front lines of medical practice. Through such programs, essentially all physicians can pursue scientific investigation throughout their professional lifetimes.

With your training--and the experience you will gain--you as physicians will be uniquely qualified to assist in continued efforts to understand and to combat the formidable health problems that remain. Such participation in intellectual inquiry adds zest to whatever you do. I anticipate that opportunities for practitioners to participate in such organized clinical research projects will expand rapidly in the next decade.

Next week, I will have the privilege of participating in a symposium with Lewis Thomas and, as always, I am looking forward to hearing the clear words of wisdom we have come to expect from him. Dr. Thomas has commented on the possible responses that modern medicine can make to the major disease problems that so far have resisted medical progress.

"The quick and easy way," he said, "is to conclude that these diseases not yet mastered are simply beyond our grasp. The thing to do is settle down with today's versions of science and technology and make sure that our health care system is equipped to do the best it can in an imperfect world. The trouble with this approach is that we cannot afford it. The costs are already too high and they escalate higher each year. Moreover, the measures available are simply not good enough. We cannot go on indefinitely trying to cope with heart disease by open heart surgery carried out at formidable expense after the disease has run its destructive course. Nor can we postpone such issues by oversimplifying the problems, which is what we do . . . , by attributing so much of today's chronic and disabling disease to the environment or to wrong ways of living. The plain fact of the matter is that we do not know enough about the facts of the matter and we should be more open about our ignorance."

But I would not wish to leave Lewis Thomas on this downbeat note. He went on to say paradoxically that there has never been a period in medicine when the future looked so bright. He amplified this thought and I will close with his words. "There is within medicine," he said, "somewhere beneath the pessimism and discouragement resulting from the disarray of the health care system and its

stupendous cost, an undercurrent of almost outrageous optimism about what may lie ahead for the treatment of human disease if we can only keep learning."[13]

And with that theme, I will close. I salute you, the graduates of the Class of 1984, and wish each of you Godspeed.

# # # #

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WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

On behalf of the National Institutes of Health, I am honored to join in extending a warm welcome to the participants in this IXth International Congress on Nephrology who have come to Los Angeles from more than 50 countries throughout the world. I also bring sincere greetings from the NIH community to our colleagues from the United States who are taking part in this important meeting.

As most of you know, the National Institutes of Health, one of the five agencies of the U.S. Public Health Service, is our Government's principal arm for biomedical research. The NIH either conducts or supports more than a third of all health-related research performed in this country by the government, academic institutions and industry.

Eighty percent of our annual budget of $4.5 billion is expended for the support of research in academic health centers, universities, hospitals and other laboratories external to NIH.

We depend heavily upon the ideas and expertise of academic scientists in carrying out our research mission, and in turn our agency is the source of funding for almost two-thirds of all biomedical research carried out in institutions of higher learning, including health professional schools. Almost $80 million of our budget is devoted to renal research.

The NIH also supports a limited amount of research in countries other than the United States. In addition, our scientists collaborate actively with research being carried out in laboratories and clinics around the world. On any given day, more than a thousand visiting scientists from more than 60 countries can be found working side by side with NIH scientists in our intramural laboratories in Bethesda.

Such extensive collaboration is an effective means for carrying out current research projects, and through such joint efforts the scientists develop vital communication links that can be of great advantage to both the hosts and the guests as they continue their scientific endeavors. In much the same way, this Congress serves as a prime means for developing and nurturing scientific communications across both disciplinary and international borders.

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*IXth International Congress of Nephrology,
Universal Studios, Los Angeles, CA, June 11, 1984.

**Director, National Institutes of Health, Bethesda, MD.

This meeting should be of substantial value to the scientists and clinical specialists who have devoted their professional careers to the study and treatment of renal disease.

But nephrology is more than a challenging medical specialty or scientific discipline. Accomplishments in this field are of great consequence to the multitudes around the world whose lives have been or may be affected by kidney disease, and although they are not present they have in the fullest sense of the word a vital interest in the basic purposes of this Congress.

You have my best wishes for a very successful meeting. Thank you.

THE IMPACT OF THE TECHNOLOGICAL EXPLOSION ON SCIENCE AND MEDICINE IN THE COMING YEARS*

Chaired By

James B. Wyngaarden, M.D.**

The topic for this discussion--"The Impact of the Technological Explosion on Science and Medicine in the Coming Years"--is wonderfully broad, permitting speakers to choose from an encyclopedia of important and stimulating topics.

I will direct my remarks primarily to research and, to some extent, the transfer of knowledge gained through research into the practice of medicine. These are matters that are at the heart of the NIH mission, which--simply stated--is "to uncover new knowledge that will lead to better health for everyone."

For centuries physicians have been able to alleviate symptoms of disease, but only in the past 50 years have the means for preventing or curing certain diseases become available. The simplicity and effectiveness of therapy are usually related to the level of our understanding of the disease process itself--its origins, its progression, and its effects. Because of the way in which research advances--through discovery along many lines of investigation--we are always confronted with great gaps in our knowledge. In recent years--as technology development has become more rapid--these gaps have taken on greater significance. The therapies stemming from incomplete knowledge--from half-way technologies, in Lewis Thomas' felicitous phrase--are often expensive and less than satisfactory.

Nowhere is the gap in our comprehension more apparent than in the case of end-stage renal disease. Dialysis prolongs the lives of patients with this fatal condition, but it provides little insight into the nature of the underlying disorder. Dialysis is expensive but does not cure the disease, reverse it, or return patients to a normal state of health. It is an imperfect solution based on an intermediate level of knowledge, but made necessary because of our lack of fundamental knowledge about the origins and processes of kidney failure, and how to prevent or cure the responsible conditions.

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*IXth International Congress of Nephrology,
Los Angeles, CA, June 12, 1984.

**Director, National Institutes of Health, Bethesda, MD.

The May 18, 1984 issue of the Journal of the American Medical Association reprinted the original 1956 article by Merrill, Murray, Harrison and Guild on the successful transplant of a kidney from one identical twin to another.[1] This pioneering effort launched a new era in medicine of internal organ transplantation, more recently extended to the heart, liver and pancreas. As with all research, the first kidney transplants made use of earlier discoveries. There had been attempts with cadaver kidneys, work with animals, and experience with skin grafting. The physicians had knowledge gained from studies of an ectopic extraperitoneal technique originated in France. In addition, the Massachusetts group was able to use extracorporeal hemodialysis to prepare the recipient for transplantation, for they had at hand a modified version of the Kolff artificial kidney. I note that the program for the Congress' meeting includes an overview of the current status of kidney transplantation. That presentation will surely include discussion of the improvements in kidney transplantation brought about by research in biomedical engineering, pharmacology, immunology, and tissue typing.

Yet even those who are currently advancing the technologies in organ transplantation and artificial organ development--whether applied to kidney disease, heart disease or other problems--would concede that if we really had sufficient knowledge, sufficient to prevent disease or reverse the disease process, these half-way technologies would be of reduced importance in our medical repertoire. Where we are resigned to rely on such technologies, it is because the seminal advances in understanding pathogenesis and pathophysiology have not yet emerged from basic studies directed at fundamental mechanisms. That is why the NIH continues to give such a high priority to basic biomedical research, for we need evermore powerful tools and explanatory mechanisms if we are to achieve adequate means for prevention of chronic and disabling diseases.

Currently, about 61 percent of NIH's research budget is devoted to studies classed as basic or fundamental. It is especially important when the research budget is in a steady state to make very careful decisions about where to place emphasis in research. The present administration has made policy statements in support of basic research by government that are the strongest ever articulated by the White House. Dr. George Keyworth, the President's Science Advisor, has said, "Basic research warrants government support because it is an investment in the future--in a better quality of life, better security, a better economy, and simply better understanding."[2]

As articulated by Dr. Keyworth, the support of basic research is a responsibility of government for the dual reason that it benefits the people and the economy of the Nation, and because there is no other substantial source for its support.[3] The bulk of support for basic biomedical research, which is conducted mainly in university laboratories, will continue to come from the Federal Government, primarily through NIH. Total national support for health R & D in 1982 was an estimated $9.2 billion. Of that total, 37 percent was supported by NIH, 37 percent by industry, and 26 percent by other Federal, state and local governments, and private non-profit organizations. But when we look at all basic health research support, which totaled some $2.8 billion, 63 percent was provided by NIH and about 10 percent by industry.

But, given the commitment to basic research and adequate funding, how can it actually be carried out? From its inception, NIH has awarded research grants based on the principle that scientists should be allowed complete freedom and independence to determine the nature, scope and methodology of their scientific pursuits. Scientific progress, we believe, results from the free play of free intellects working on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown. The key instrument NIH has used to provide support for free inquiry is the research project grant--the investigator-initiated grant--a project proposed to the NIH by the individual scientist and approved through the NIH peer review system. This type of grant is the mainstay of the Nation's biomedical research scheme, for we believe it fosters creativity and excellence. The most exciting and important research findings emerge from a flexible system that permits diversity and allows individual scientists the freedom to pursue scientific leads according to their own creative energies.

While I have devoted a good deal of my remarks so far to the importance of basic research, it is clear that it would be a great mistake to put all our resources into studies of fundamental mechanisms and processes. Scientists need to be supported in expanding frontiers of knowledge across the entire spectrum of research, which must also include application of new knowledge to practical problems. We need to take advantage of biomedical research opportunities wherever they arise. In cancer research, for example, there is a great deal of excitement at basic levels of investigation. Advances seem to be occurring almost weekly in the area of oncogenic transformation in cancers. It may be possible to find a way to block the transformation of the latent oncogenes. Such findings would introduce entirely new strategies of therapy. Meanwhile, we see improving cure rates for many kinds of cancers due to refined surgical, radiological and chemotherapeutic approaches. These treatments--despite the fact that they offer cure to many people--could still be called "halfway technologies" similar to dialysis and transplantation. But they have provided--up to now--our best weapons against cancer. And we will continue to employ them while we await the improved technologies that will emerge from current basic efforts. Simultaneously, we are also emphasizing new prevention strategies based on new information on dietary factors that appear to be associated with higher cancer rates.

I could expand this list to other fields of medicine, but perhaps the examples from kidney disease and cancer will suffice to define the issues that we face.

The title of our symposium today clearly points us toward the future. It is clear that if we are to sustain momentum in our accumulation of basic biological knowledge, and if we are to continue to translate this knowledge into applicable technologies, then we need to concentrate now not only on generating a supply of well-trained, creative, and innovative researchers for the coming years, but also on improving the level of scientific competence of the health care profession generally.

The math and science that students learn in elementary and secondary school underpin our future in research and technology. Our public education system must improve its preparation of high school students for living in a technological age. Early education in the sciences is important in another way--often that early exposure to the excitement of science can motivate top students to take up careers in scientific research. I also believe that physicians generally will need strong science backgrounds if they are to serve their patients well in capitalizing on the coming advances of the technological revolution.

I am also concerned with our source of clinical investigators, our physician/scientists for the future--and this is a direct responsibility of the NIH.

We need physician/scientists capable of applying basic research to the practice of medicine. This is a most exciting type of research, requiring someone who is both medically knowledgeable and scientifically trained. We also need clinical investigators to move the path of inquiry in the other direction--from "bedside to bench." In this type of research, the clinical question is the central force of the investigation, yet basic knowledge is gained. But, given the rapid pace of advance of research, the task of becoming scientifically competent is growing more and more difficult for clinicians.

Science has become complex, the methods intricate, and the required training long. In my view, the burgeoning of biomedical knowledge in the past decade has forced the progressive professionalization of biomedical research, in particular of clinical research. I hope there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training in the information, concepts, and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

The importance of more and better quality training for our future physician/scientists cannot be overemphasized. Recent analysis by NIH has indicated that for M.D. postdoctoral trainees, the longer they have trained, the more likely they are to apply for and receive an NIH research grant; unless they have a minimum of three years of research training, they usually are not successful in competing for grants. The most successful applicants of all are those with combined M.D./Ph.D. degrees. Their success rates are higher than of those with the Ph.D. degree and much higher than of those with the M.D. degree who now lag far behind, chiefly I believe because of inadequate research training. For example, we have found that in programs where the median length of training is only 12 months, only 20 percent of the M.D. graduates apply for grants and only 10 percent are successful.

There is a great deal of interest in this country--expressed by the Administration, by the Congress, and by the scientific community in finding means to provide for future clinical investigators. For its part, the NIH has an array of training and career development programs that are especially designed with M.D.'s in mind. Because we are convinced that early exposure to research is an important factor in attracting bright and dedicated

students into biomedical research, we have set up a number of programs whereby students can supplement their medical education with research experience. For young physicians who are willing to make a major commitment to research, we have developed a new program--the physician/scientist program--which provides five years of support, including three years of training in basic research and an additional two years in a clinical setting. Although the program has just entered its first candidates, it is hoped that the length and kind of training provided will help to ensure a supply of physician investigators to participate in the "new" scientific era.

Of course, the ultimate goal of research is to improve health by moving relevant research findings into the health care realm. The term used for this occupation is often "technology transfer." Technology transfer encompasses an amazingly complex collection of pathways. It is hard to imagine that anyone who sets out to design a system for "technology transfer" could devise a system so complex in its totality and so simple in its individual parts.

Clearly, the physician and the physician/scientist play key roles in technology transfer in this country. And the recent rapid developments in science and technology have placed additional new demands on those in medicine. The "new age of medicine" will require a cadre of scientists with medical knowledge, clinical skill, and research expertise to capitalize on the biotechnological revolution and to carry its results into clinical practice. The work going on now in the Lesch-Nyhan syndrome is just an example of what is to follow in other areas--scientists have recently cloned the gene for HGPRT and have been able to insert it into defective cells in vitro with success in correcting the deficient function. The Lesch-Nyhan syndrome may be the first candidate for gene therapy in humans, with other similar genetic metabolic diseases to follow. With these kinds of opportunities and many others bred of the bioscientific revolution, the burden upon clinicians and scientists is great and challenging. Highly specialized training will be required of professionals working in these areas.

Over the past decade, the NIH has taken an increasingly active role in communicating the findings of research to the health professional community. The output of biomedical research covers a very broad spectrum ranging from discoveries at the frontiers of biology to readily applicable means of disease prevention, diagnosis, or treatment. Each element in the array of findings is useful either to the research scientist or to the clinician, or to both. However, the busy practitioner would not only be inundated by the sheer volume if the full output of published results were channeled to him or to her, but would not have time to identify those findings that might be applicable to practice. For this reason, it is essential that there be a sorting out process and that communications efforts be concentrated on the relatively small portion of current research output that is ready for use by the health professional in patient care. There are many channels of communications with the practitioner--some are highly structured, others are patterns of custom.

Academic health centers are key communicators. They take seriously their responsibility for the continuing education of their own graduates and health professionals practicing in their geographic area. Specialty and professional organizations support many individual programs of continuing education as well. This Congress is an example.

The NIH now engages in a very considerable amount of direct communication with practicing health professionals. During the average year, it sponsors about 100 seminars and other meetings for practicing physicians which are annually attended by an aggregate of about 10,000. In a typical year, the NIH responds to more than 80,000 inquiries from physicians, either by mail or telephone, and prepares more than 170 different publications for the use of physicians. In addition, the NIH publishes some 135 different informational brochures for the physicians to use in patient education. Three-quarters of a million copies of such publications are distributed upon request to practitioners in a normal year.

The National Cancer Institute's Program of 20 comprehensive cancer centers scattered throughout the Nation exerts a significant impact through effective cancer control, demonstration and outreach programs. These centers are focal points for community efforts to assure widespread use of the best available methods for early detection and diagnosis of cancer and dissemination both at the lay and professional levels. The centers are designed to be places to which individuals and their physicians can turn for information, help and advice.

The multidisciplinary general clinical research centers supported by the NIH at 75 medical centers have served as demonstration and communication centers for more than two decades.

NIH Consensus Development Conferences provide a neutral forum for a thorough public discussion of the scientific pros and cons of new modes of treatment or preventive measures as well as of long-established practices about which doubt or question may have arisen. Over 40 such conferences have been held. At each, a consensus panel of experts in the relevant disciplines, usually including lawyers and ethicists as well as scientists with direct interest in the problem under discussion, sit as a kind of jury. They hear statements from responsible spokespersons representing differing points of view on the subject under discussion. Usually the testimony lasts for two days, following which the panel attempts to develop a statement of consensus on the question under discussion.

Recent conferences have covered such diverse subjects as "bypass surgery for morbid obesity"; "hip joint replacement"; "liver transplantation"; "uses of ultrasound imaging in pregnancy"; and "analgesic-induced kidney disease."

Results of the consensus conferences are published in the Journal of the American Medical Association, as well as other medical journals. Copies of the consensus statements are mailed promptly to some 22,000 physicians nationwide who have asked to be given such information. The primary purpose of the consensus conference is to aid in the transfer of research-derived information to the practicing health professional, but there has also been substantial public interest in this activity.

A highly important and unique component of the National Institutes of Health that constitutes a critical instrument for dissemination of research information is the National Library of Medicine. The Library collects, organizes, and makes available biomedical information to investigators, educators and practitioners, and carries out programs designed to strengthen medical library services in the United States and in other countries. As the central resource of the existing National Biomedical Information System, it is an essential element in the public health establishment in our country.

The Library's comprehensive collections and information services at its main headquarters on the NIH campus in Bethesda are used extensively by health professionals and health science students. But more importantly, the NLM serves as a National resource for all U.S. health science libraries. Lending of books and other services are provided through a regional medical library network serving well over 2,000 hospital and medical school libraries.

The Library's computer-based medical literature and analysis retrieval system (MEDLARS) was established to permit health professionals throughout the Nation and in many parts of the world to achieve rapid access to NLM's vast store of biomedical information.

As a summary to my contribution to this panel discussion, permit me to return for a moment to the theme of the earlier portion of my talk, about the importance of the reductionist as well as the synthetic approach to answering fundamental questions in biology--that process of exploring details, and the details of details, until all the smallest bits of the structure, or the smallest parts of the mechanisms, are exposed to scrutiny. This has been called the bioscientific strategy of medicine.

Critics of the bioscientific strategy have claimed that the great advances that have dramatically reduced mortality rates consist in the improvement of the environment, the correction of malnutrition, and the control of infectious diseases through immunizations and antimicrobial agents, and that the relevant medical breakthroughs largely occurred before the prodigious expansion of Federal support of biomedical science began in the early 1950's. They contend that the enormous expenditures in biomedical research have produced too little in the way of medical advance to justify their continuation, and have instead fostered the development of an extremely costly technology which has had only a minimal effect upon mortality statistics. They propose that the bioscientific strategy of medicine should be replaced by an ecologic strategy for health.

I prefer a different analysis. First, a bioscientific strategy for medicine and an ecologic strategy for health are not mutually exclusive and, in fact, NIH has vigorously supported both approaches. Also, many major advances have occurred since 1950 that have revolutionized the outlook in individual diseases or disease groups, as a direct result of scientific discoveries. Furthermore, the expansion of the knowledge bank of the last quarter century justifies great optimism for the eventual control and cure of major diseases and the possible elimination of premature death from illness.

The list of human diseases for which there are as yet no definitive measures for prevention or cure is still formidable. Fresh insights into the nature of these diseases are needed. These insights can come only from continued basic research. We do not have an abundance of scientific information locked in the laboratory merely awaiting a new emphasis on human application. The essential pieces of background information are not merely awaiting assembly; most have yet to be discovered.

I believe that the emphasis on the bioscientific strategy will lead to improved understanding, and that with it will also come a strengthened scientific basis for prevention and for ecological strategies for health, as well as to a progressive reduction in the financial burdens of our present state of half-way technologies.

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FAREWELL REMARKS TO

DR. LESTER B. SALANS*

BY

JAMES B. WYNGAARDEN, M.D.**

Les, I speak for your many friends at NIH when I extend our warmest wishes to you as you enter a new and exciting phase of your career.

In moving to New York, however, you may be missing a truly spectacular biological event at Bethesda--the mitosis of an institute. At this time we are certainly in the prophase if not the metaphase of that happening in whose final stage the parent cell becomes completely divided into two cells, each having a reorganized nucleus. I would think that you as a scientist would have some regret about not having an opportunity to observe this fundamental process at first hand.

Also, I think I should tell you in the candid spirit of friendship that we have been searching the U.S. Code, the Departmental Regulations, and the Standards of Conduct for some legal way to put a moratorium on you, Tom Chalmers, and others for the purpose of preventing Mt. Sinai from doing any more recruiting at NIH just now. We have even checked the NCAA rules about the matter. Someone has suggested an even higher code--one that should be well known at Mt. Sinai--namely, the Ten Commandments.

Could we ask any less, Les?

And we wish you well.

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*National Institutes of Health, Wilson Hall, June 19, 1984.

**Director, National Institutes of Health.

REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

It has been two years since the last time I welcomed the first NIH Extramural Associates Workshop in June 1982. That meeting was jointly sponsored by NIH and your institutions, just as this one is.

Today, I am delighted to meet again with the associates and the presidents of the extramural associate institutions. Permit me to say to the latter group that we are especially pleased to have so many presidents with us because your presence speaks strongly of your interest in becoming active participants in the NIH biomedical research endeavor.

The Extramural Associates Program continues to expand and has now established important ties with 68 minority and women's institutions in 26 states across the country and in Puerto Rico since the program's inception in 1978.

I regard these developing ties between your institutions and the National Institutes of Health as an important part of NIH progress toward broadening the family of grantees and expanding the opportunities for investigator-initiated research.

From the NIH perspective, it would be difficult to overestimate the importance we attach to our partnership with academia. Fully 80 percent of the $4.6 billion being requested for the NIH next year is allocated for grants and contracts to support research and training at more than 1,200 professional schools, colleges, universities, laboratories, hospitals, clinics, and other institutions. Academic institutions, however, receive well over two-thirds of the total amount that NIH awards in grants and contracts each year.

The multiple advantages realized from Federal support for the conduct of research at academic institutions was demonstrated conclusively during World War II. In the succeeding years, the NIH/academic partnership for biomedical research has been extremely productive. The resultant surge of productivity that has taken place in the sciences in less than a generation is without precedent and is gathering strength.

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*Extramural Associates Workshop, National Institutes of Health, June 25, 1984.

**Director, National Institutes of Health, Bethesda, MD.

The associates program was designed as a means for assuring that in our partnership the representation from the academic side be fully inclusive. Insofar as we are not joined in the research effort by all of the resources of talent and energy in this country, we fall short of our potential.

It is vital to our success for you to participate as partners in the accomplishment of these aims and to link NIH research objectives with the needs and the health concerns in your communities and within your institutions.

Your efforts will require periodic updating regarding research policies and procedures and a strong commitment on your part to expanding and developing the research capabilities of your institutions and faculty members.

The greatest part of the NIH budget, by far, goes to the funding of investigator-initiated research. Such funding is awarded in response to research proposals submitted by individual scientists within academic or other institutions that assume important responsibilities for fiscal stewardship and compliance with essential regulations.

We welcome new investigator participation. The success of minority and women investigator-initiated research will continue to expand through leadership, the commitment of time and resources, and the maximum utilization of your faculty members and your extramural associates.

We are hopeful that each president has come to this workshop in order to develop a broader understanding of NIH and what must be done by your institutions to take full advantage of opportunities in biomedical research that are now available at the National Institutes of Health.

Many of you are NIH grant recipients through the MBRS (Minority Biomedical Research Support Program, DRR), the MARC (Minority Access to Research Careers Program, NIGMS), and through NIH institutional training grants. We want you to increase your participation in all aspects of NIH research, and we intend to continue to make opportunities available to women and minority investigators and newly developing scientists.

The recent pace of discovery in the field of biomedical research is explosive. This is especially true in the realm of molecular biology. Exploitation of our rapidly expanding knowledge in this field is opening new vistas for improvements in prevention, diagnosis, and treatment of many diseases. And even more exciting are the tantalizing insights gained from the use of the new techniques in the study of disorders ranging from cancer to Huntington's disease.

It is an exciting time--one that challenges each of us with unusual opportunity for significant accomplishment. We are hopeful that during this workshop you will find ways to broaden the participation of your various institutions in the widespread effort to uncover new knowledge that will lead to better health for everyone.

I extend to you a hearty welcome and hope that you will enjoy as well as profit from your visit to Bethesda. You have my sincere best wishes for a successful workshop and for your continuing success upon return to your respective institutions.

# # # #

THE FUNDING OF BIOMEDICAL RESEARCH*

by

James B. Wyngaarden, M.D.**

Within the lifetime of most of us and the memory of some of us, the role of the physician has undergone a revolutionary change. Viewed in retrospect, we can now see that prior to the mid-thirties, the physician was essentially an experienced spectator and well-versed commentator on the course of natural phenomena. Practitioners of medicine had become highly sophisticated observers, skilled in diagnosis. Based on accumulation of medical experience, they could forecast with reasonable accuracy the future course of an ailment. Accurate diagnosis became the central purpose for medicine. As the methods for diagnosis improved, patients and their families could be told not only the nature of the illness but also with some reliability how it was most likely to turn out, but that was about all that a physician could do.

This essentially passive approach to the practice of medicine was in fact a major improvement over the centuries-old habit of treating everything with something, often with harmful results.

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*Keynote Address, American Association for Clinical Chemistry, Washington Convention Center, Washington, D.C., July 30, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

Lewis Thomas has stated his belief that the true beginning of the revolution in medicine was a hundred years before penicillin. "The revolution," he said, ". . . did not begin with the introduction of science into medicine. That came years later. Like a good many revolutions," he added, "this one began with the destruction of dogma. It was discovered sometime in the 1830s that the greater part of medicine was nonsense."[1]

He noted that over the succeeding decades the traditional therapeutic ritual of medicine was given up, and what came to be called the art of medicine emerged to take its place. In spite of the doctor's inability to do much to prevent or terminate illness, he was depended upon to explain illness, to relieve anxiety, and to be on hand.

In the last decades of the nineteenth century the basic knowledge needed for the science of medicine began to be sought and found. The predecessor to the National Institutes of Health had its beginnings in this same period. Though quite small, the Laboratory of Hygiene, established in 1887, was a part of the movement to study in detail the newly discerned roles played in disease by bacteria and viruses. The first Director of the Laboratory, Dr. Joseph J. Kinyoun, had learned the uses of tuberculin under Dr. Robert Koch in Berlin, and at the Pasteur Institute in Paris had studied the newly developed methods for preventing rabies.

In writing about this period in medical history, Lewis Thomas reminded his readers that ". . . It needs emphasizing that it took about 50 years of concentrated effort in basic research to reach

this level," and "If this research had not been done, we could not have guessed that streptococci and pneumococci exist, and the search for antibiotics would have made no sense at all."[2]

This lesson was not lost on the scientists and Government leaders who were involved in the total mobilization of national resources required by our entry into World War II.

Vannevar Bush, Director of the wartime Office of Scientific Research and Development, observed that "the striking advances in medicine during the war have been possible only because we had a large backlog of scientific data accumulated through basic research in many scientific fields in the years before the war."[3] He reported at the end of the war in 1945 that the death rate for all diseases in the Army, including overseas forces, had been reduced more than twentyfold from 14.1 per thousand in World War I to 0.6 per thousand in World War II. He noted that such ravaging diseases as yellow fever, dysentery, typhus, tetanus, pneumonia, and meningitis had been all but conquered by penicillin, the sulfa drugs, insecticides, better vaccines, and improved hygienic measures.

Then turning his attention to the years ahead, Dr. Bush enunciated what might be a mission statement for the National Institutes of Health in these words: "Notwithstanding great progress in prolongiong the span of life and in relief of suffering, much illness remains for which adequate means of prevention and cure are not yet known. While additional physicians, hospitals, and health programs are needed, their full usefulness cannot be attained unless we enlarge our knowledge of the human organism

and the nature of disease. Any extension of medical facilities must be accompanied by an expanded program of medical training and research."[4]

Summing up his report on the war against disease, Vannevar Bush then made a key recommendation. He said, "It is clear that if we are to maintain the progress in medicine which has marked the last 25 years, the Government should extend financial support to basic medical research in the medical schools and the universities through grants both for research and for fellowships."[5]

This sentence encompasses the policy amplified and acted upon by successive Administrations and Congresses in the intervening years. Its prime expression is the National Institutes of Health.

While Dr. Bush recognized the necessity of Federal support for research, he did not foresee the magnitude of this Federal academic partnership. The financial support extended by the Government for biomedical research in nonfederal academic institutions, hospitals, and other laboratories has grown very rapidly. In 1946, the total NIH appropriation was $3.4 million. That is less than 0.1 percent of the current budget of about $4.5 billion.

This brings me to the announced subject of my remarks today, "The Funding of Biomedical Research."

Bob Habig asked me to give him a title for this address some seven months ago, in late December. That is the season of the year when the President's annual budget request is being finalized, and agencies like the NIH are engrossed in preparing the enormous amount of detailed information to be submitted to the Congressional Appropriations Committees in support of the

Administration proposal. It is not remarkable that "funding of biomedical research" was on my mind at the time.

Rather than engaging the subject in its totality, however, I will confine my discussion mostly to the programs I know best--the activities of the NIH--that constitute two-thirds of the total Federal commitment to biomedical research. And, instead of presenting an analysis of the current NIH budget or making a daring prediction on what next year's will be, I will highlight certain general policies and concepts that have evolved during the past 40 years of our operations.

The decision was made in 1945 that biomedical research was more than appropriate as an object for continued Government support. Further, it was concluded that a major element of the Federal effort would be to support most such research in America's medical schools and universities.

As a consequence, forty years later, some 1,300 academic medical centers, research hospitals, laboratories, and other scientific institutions share in the almost $3.6 billion in grants and contracts awarded by the NIH in support of research and research training. These extramural awards represent 80 percent of the total NIH budget. Two-thirds of our extramural expenditures are devoted to project grants made in response to applications initiated by individual investigators. The emphasis that has been given to investigator-initiated grants has continued over such a long period that the awards are commonly known as "traditional" NIH grants.

From the NIH perspective, these awards have proved to be highly effective means for gaining direct access to essentially the entire American scientific community and thus to the creative ideas of its members. For the researchers, the grants are the sources of support for meritorious research that otherwise they might not be able to conduct. Further, the consistent availability of such project support gives some assurance to a young scientist that a career in biomedical research can be a realistic option.

For these reasons, the NIH has made a special effort to maintain predictable levels of funding for investigator-initiated grants so that predictable numbers of such grants could be made. Currently, more than half our total budget is allocated to these grants. The priority given to project grants over the past decade has at times diminished the proportion of resources available for other important research-related programs, including training.

In the face of these side effects, we remain convinced of the central importance of the investigator-initiated research project as a mechanism for stimulating and sustaining the best biomedical research. Currently, nearly 10 percent of our investigator-initiated research projects are being conducted by first-time principal investigators, scientists who had not previously directed research projects funded by the NIH. We are convinced that the total research effort of our agency is greatly strengthened by this tithe, this continuing infusion of new investigators and their fresh ideas. We must never lose sight of the fact that the vigor of the research enterprise requires constant renewal

through acquisition of the commitment of young scientists. It is for this reason that we consider research training so critically important to the future of research. During this year, I have been devoting substantial time and thought to an examination of our NIH training activities for the purpose of determining if the traditional training support mechanisms continue to meet current needs and if new ones would be beneficial.

The general consideration of how best to fund biomedical research, of course, must take into account many issues in addition to mechanisms of support; for example, the question of how best to organize an agency for the conduct and support of biomedical research. This is a live issue that has been confronted frequently since the modern NIH came into being in the 1940s.

Within the biomedical scientific enterprise itself, during recent years there has been a gradual change having profound implications. Nobel laureate Arthur Kornberg recently called attention to the "confluence of the many discrete and previously unrelated medical subjects into a single unified discipline." He observed that "anatomy, physiology, biochemistry, microbiology, immunology, and genetics have now been merged and are expressed in a common language of chemistry."[6]

It is ironic that in the presence of this confluence of the scientific disciplines, there are increasing pressures on the NIH for fragmentation through the creation of new institutes or organizational entities each having a relatively narrow focus on a particular set of health problems. Such movements gain much of their strength from and indeed are an expression of the public

confidence in the power of research. The names of the 11 NIH Institutes bear witness to the power of specificity. Most of them were established in response to the public's desire that more research be conducted on particular families of disease. The current pressures are also an understandable reaction by segments of the biomedical community to their perception of need for more funding in their areas of research.

The NIH and the Department of Health and Human Services have opposed legislation for the creation of new Institutes and for the establishment in statute of favored status for specific research programs. Our oppostion to these proposals is based not only on their adverse effects on administrative costs and flexibility, but also because the compartmentalization they establish is counter to the direction in which science is moving. At a time when we can confidently predict unusually rapid movement in science but cannot predict just where that progress will occur, we need the maximum flexibility for marshaling finite resources for the support of science.

In June of 1983, however, we asked the Institute of Medicine of the National Academy of Sciences to make an objective study of the NIH and to recommend the establishment of standards for determining the need for an substantial change in the organizational structure of the agency. We expect the study to be completed and to have a report from the IOM by November of this year.

At this time, the Federal Government conducts or supports 52 percent of health-related research and development in this

country. Industry is responsible for 39 percent, with foundations and voluntary health agencies funding less than 10 percent.

The dominant role of the Federal Government is at the same time complementary and, to a degree, is determined by the interests of the other participants. Industry, for good reason, gives high priority to developmental and product-related research. The organization of voluntary health agencies is categorical--that is, disease specific--and their funds are raised in the name of cancer, heath disease, birth defects, etc. There is little likelihood that voluntary agencies could be successful in raising substantial funds for basic research alone. For industry, economic pressures strongly favor priority for applied and developmental rather than basic research.

I should note, however, that in the past decade there has been a marked increase in industrial support for research conducted in academic institutions so that a third partner has joined the long-standing Federal/academic cooperative research relationship.

Nevertheless, it is our belief--a belief shared at the highest levels in the Administration--that the Federal Government will continue to be the principal source of funding for basic research.

In the material submitted by the President's Office of Management and Budget in justification of the 1985 budget, the policy regarding research was stated in these words: "The 1985 budget reflects the high priority which this Administration continues to give to the support of basic research across all

scientific disciplines. Additional support for basic research is based on the premise that the long-term economic strength of the nation and continued improvement in the well-being of its citizens requires a sustained investment in basic scientific research."[7]

The progress in the last two generations in the application of science to health has stimulated expectations. People today are being taught to expect good health care. In the past, throughout history, man has tended to accept illness, plagues, and personal injury as "normal." This is no longer the case, and this new attitude represents a change just as profound and revolutionary as the change in the role of the physician of which I spoke earlier. The newfound ability of medicine to control or even to eradicate disease--a direct legacy of research--has brought into being new human expectations and even demands. Inevitably, such a development has major economic implications.

The complex calculus of cost/benefit analysis of medical progress is illustrated in an example cited 20 years ago by Dr. Lowell Coggeshall, then Vice President for Medical Affairs of the University of Chicago. Writing in a report on medical education, he compared costs of the old and new medicine. "Once," he said, "it took only one doctor to resign himself and the child's parents to the inevitable death of a 'blue baby'; it now takes a team of medical specialists and auxiliary personnel to correct the congenital abnormality of a baby's heart to insure the child a normal lifespan. More than 100 medical specialists, nurses, and skilled technicians are involved in preparations for and performance of the operation and in the postsurgical care of the patient."[8]

This example points to the fallacy inherent in using dollars to measure the costs versus benefits of medical innovations. Basically, the cost of research and the health benefits it makes possible are incommensurable.

However, in the course of seeking funds for the research enterprise, persons in positions like mine are constantly being called upon to justify the purposes of the substantial investment required. I do not quarrel with the need to make the case for the expenditure of public funds for the support of research. In justifying to the Congress and the Administration our request for funds, my colleagues and I have emphasized the intangible and incalculable human benefits--the improvements in the quality of life--that have come from research, and frankly, I cannot suggest a better reason for the current national investment in biomedical research and development.

But there is another effect of biomedical research, a benefit that is perhaps more evident to economists than to bioscientists. We are not accustomed to viewing biomedical research as a financier might scrutinize the cost/benefit track record of an industry.

A five-years study attempting to quantify the worth of biomedical reserach was conducted in the late seventies. The results were published in 1979 in a book by Selma J. Mushkin, titled "Biomedical Research: Costs and Benefits." The study addressed the question, "Is the public getting an appropriate return for the multibillion dollar yearly expenditure on health research?"

The answer was an emphatic "yes" when the measures used include actuarial estimates of the dollar value of the productivity of the lives saved and the years of sickness averted. For the 75-year period beginning in 1900, the ratio of total cumulative benefits to total research and development costs was about 13 to 1. In more recent years since 1930, the ratio was 5 to 1. The recent, somewhat lower but still spectacular return includes the high level of basic research during the past 40 years whose payoffs are certain to affect future ratios of benefits to costs.

In just one area, recent events have highlighted other beneficial and tangible effects of the national investment in biomedical research. For example, in the past seven or eight years, a totally new industry has emerged from the utilization of recombinant DNA, cell fusion, and related technologies that were developed with public funds. In just one year--1983--a billion dollars was invested by the private sector for the commercialization of the products of these new discoveries.

In the context of these economic benefits, we encounter a paradox; namely, that a substantial number of medicine's discoveries in recent years have <u>increased</u> rather than <u>decreased</u> the cost of medical care. This is an aspect of the economics of research about which there has been considerable public discussion of late. Writing in <u>The Washington Post</u> last month, staff writer Spencer Rich summarized the predictions of a number of experts in health care and research as follows: "Costly medical innovations such as heart and liver transplants and expensive futuristic diagnostic techniques could plunge the nation into vast additional

health expenditures over the next generation and confound efforts to rein in health outlays."

When considering this question, however, we must not forget that each of these innovations represents for the patients involved and their families supremely important progress, hope, and benefits that cannot be measured.

Recently, I attended the International Congress of Nephrology at which there was much discussion of the beneficial effects of technology as well as its adverse effect on the costs of medical care. During a press conference in a discussion of the rapid increase in the cost of medical care, I speculated facetiously that someone will someday suggest to the Office of Management and Budget that the best way to control cost is to shut down the NIH. This was reported in The Los Angeles Times. About two weeks later, I received a letter from Harry Schwartz, long with The New York Times, and now a writer and lecturer on medical issues. He reminded me that my prediction had been fulfilled before I made it--that he had been the someone who would someday suggest shutting down research to save on the cost of medical care. He sent me a copy of an article of his that appeared in The Wall Street Journal, April 3. "Do we really want medical progress," the article began, "or should we start thinking seriously of closing the National Institutes of Health and other public and private facilities now doing research to cure diseases and prolong lives?"

In his letter to me, he repeated what he calls Schwartz' first law of medical economics, that reads, "In health care, the ultimate economy is death."

In the face of all this, I remain an optimist and believe that, if we persist, one by one these expensive technologies t are now life saving will be rendered as obsolete as the iron l but we must continue to search.

In closing, permit me to use a familiar quotation from Le Thomas, a truth about which we need to be reminded periodicall Here are his words: "I say that we must continue doing biomed research on about the same scale and scope as in the past 20 years, with expansion and growth of the enterprises being dependent on where new leads seem to be taking us. It is an expensive undertaking . . . but it is still nothing like as expensive as trying to live with the halfway technologies we ar obliged to depend on in medicine today; if we try to stay with these for the rest of the century, the cost will go through the ionosphere."[9].

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REMARKS*

by

James B. Wyngaarden, M.D.**

On behalf of the National Institutes of Health (NIH), I am honored to join President Iggo (U.K.) and Dr. Stjernswärd (WHO) in welcoming you--especially our foreign visitors who have come to Seattle from more than 50 countries throughout the world. I am appearing before you as a minor expert on the subject of pain, having experienced one of my recurring encounters with renal colic a few weeks ago. "But the oddest thing about [pain]" (as Peter Fleming observed in his essey "On Pain") "is that despite its intensity, despite its unequalled power over mind and body, when it is over you cannot really remember it at all." And how fortunate that is! This meeting is bound to be a very stimulating one--as demonstrated by the scientific content of the papers to be presented. It is doubly exciting because of the steady progress this IVth World Congress on Pain represents. The study of pain, the treatment of pain, and our commitment to continued efforts to combat pain have come a long way in just the ten years since the establishment of this group in 1974.

I am happy to note that NIH has been involved from the very beginning, having sponsored, along with the University of

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*IVth World Congress on Pain, Seattle, Washington, September 1, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

Washington, the 1973 International Symposium on Pain at which the plans for the International Association for the Study of Pain (IASP) were formulated. The IASP is a unique organization, its membership covering a broad sweep of disciplines in the basic, behavioral, and clinical sciences, and comprising an equal number of Ph.D. and M.D. scientists. Because of its composition, this organization offers an unusual opportunity for discovery in science and rapid clinical application. This organization has been the channel for an infusion of modern science into various areas of clinical practice. Moreover, many basic scientists have been stimulated through this organization and such meetings to apply their techniques and insights to an examination of questions surrounding pain. Regrettably, in recent times science and clinical practice have become more and more specialized and therefore compartmentalized, leading to impediments to communication. It is a major accomplishment that this society has gone the other way and broken down barriers to communication.

Of course, this didn't just happen. The advances made in making pain a high priority concern in this country and elsewhere are largely due to the effort of your founding father and past president, Dr. John Bonica. He has stimulated the growth of pain clinics in this country; he has moved the problem of pain toward becoming a national concern. He has also worked hard to bring this matter to the attention of the general public. In addition, Dr. Bonica has long been a friend of NIH and a champion of the need for continued research--including basic research--relating to pain.

As most of you know, the NIH, one of the five agencies of the U.S. Public Health Service, is our Government's principal arm for biomedical research. The NIH either conducts or supports more than a third of all health-related research performed in this country by the Government, academic institutions, and industry.

Over 80 percent of our annual budget of $4.5 billion is expended for the support of research in academic health centers, universities, hospitals, and other laboratories external to NIH. We depend heavily upon the ideas and expertise of academic scientists in carrying out our research mission, and in turn our agency is the source of funding for almost two-thirds of all biomedical research carried out in institutions of higher learning, including health professional schools. The NIH also supports a limited amount of research in countries other than the United States.

NIH has always supported and conducted research directly relating to the problem of pain and in scientific areas fundamentally relating to pain: neuroanatomy, neuropharmacology, etc. In the past ten years or so, that interest has become better identified with the phenomenon of pain per se. In addition to uncountable seminars, workshops, and lectures relating to scientific and clinical aspects of pain, NIH in 1979 held a major consensus development conference entitled "Pain, Discomfort, and Humanitarian Care" to review the present status of scientific information and to identify areas that should receive additional attention. NIH also participated heavily in a Public Health Service/American Medical Association Conference on "Care of Patients with Severe Chronic Pain in Terminal Illness" in 1983

and was lead agency for an HHS Committee for the Alleviation of Pain and Discomfort. The recommendations and activities of this committee have since largely been absorbed into the operating agencies such as the Food and Drug Administration, NIH, and the Alcohol, Drug Abuse, and Mental Health Administration. I might add that Dr. Bonica was involved in--indeed was a driving force behind--several of these activities.

As mentioned earlier, NIH has been and remains committed to the support and conduct of research relating to pain. The NIH Pain Clinic--the only multidisciplinary pain clinic in the United States solely devoted to research--is flourishing under the leadership of one of your members, Dr. Ronald Dubner, of the National Institute of Dental Research (NIDR). Opened in 1983, the Pain Clinic is the center for scientists from the NIDR, working in collaboration with investigators from other NIH Institutes, to conduct studies of acute and chronic pain, to generate and expand knowledge about mechanisms and treatment of pain, and to develop better ways to assess pain. This new clinic enables all NIH researchers and clinicians to pool their knowledge and exchange ideas about the pathophysiology and treatment of pain.

Extramurally, nearly every NIH Institute supports studies directly and indirectly relating to pain. A recent computer printout of support in this area shows the National Institute of Neurological and Communicative Disorders and Stroke--with its interest in the neurosciences--and the National Institute of General Medical Sciences--with its interest in anesthesiology, trauma, and burn--to be the greatest supporters of research

relating to pain, with the National Institute of Dental Research--despite its smaller budget--next in order of level of support. The National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Institute on Aging, of course, also support pain research as do, though to a lesser degree, the Division of Research Resources, the National Eye Institute, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, and the National Institute of Child Health and Human Development. The printout shows a level of nearly $20 million devoted primarily to pain research (including figures from the National Institute of Mental Health and the National Institute of Drug Abuse). Adding projects with a secondary emphasis on pain research brings that total to about $45 million. I must add that these figures were developed through a computer search based on chosen terms and the figures might differ--up or down--if projects were looked at individually. Of course, in NIH's view, this is just the tip of the iceberg, for if you counted all the basic work relating to pain--all the work in the neurosciences, for example--the figure would be much greater.

It is in the area of basic research, I think, that NIH makes its largest contribution. The NIH has committed itself to the support of basic research because we see it as the only way to revise our imperfect state of knowledge in biobehavioral sciences.

We have a long way to go: we need to elucidate the mode of action of various types of pain receptors; we need investigations of the anatomy, physiology, and neurochemistry of CNS pathways as modulators in pain sensitivity; we need to characterize further

opioid peptides and receptors in the nervous system; and we need to develop techniques for measuring and describing pain experiences under clinical and experimental conditions. But science--especially neuroscience--is in such a growth state right now, due to the availability of new and powerful research tools, that advances can be expected. We now have sensitive techniques in neuropharmacology, neurochemistry, and immunocytogenetic chemistry to advance our studies. We can now use monoclonal antibodies to try to identify new transmitters in pain pathways and their receptors. Recent advances in genetics allow us to use complementary DNA to synthesize neurotransmitter peptides and learn about precursor substances in pain.

While I have given emphasis to the importance of basic research, it is clear that it would be a great mistake to put all our resources into studies of fundamental processes and mechanisms. Scientists need to be supported in expanding frontiers of knowlege across the spectrum of research, which must also include clinical and applied studies.

Before I close, permit me to mention another matter that is important to the continued growth and accomplishment in your area of interest, for I note in the program a large number of papers involving research on animals. The possible erosion of public support for use of animals in research is a matter of deep concern. It is incumbent upon us scientists to strive to build wider consensus concerning the policy for humane care and use of laboratory animals. The Federal Government cannot on its own adequately deal with the public pressures. It is the responsibility of

institutions, investigators, and professional societies such as this to become more active in responding to questions about the need for animals in research and appropriate safeguards. Those who actually conduct research involving animals should be able to explain clearly to the public why the animals are absolutely necessary in the given experiment and why the experiment itself is important.

In closing, I offer my best wishes for a successful meeting. The program promises great diversity and a comprehensive approach to the study and treatment of pain. This meeting will surely serve as a prime means for developing and nurturing scientific communications across both disciplinary and international borders. It should be of substantial value to the scientists and clinical specialists who have devoted their professional careers to the study and treatment of pain.

But this is more than just a challenge and opportunity for the medical specialties and scientific disciplines involved. Accomplishments in the area of pain are of great consequence to the multitudes around the world whose lives have been or may be affected by chronic or acute pain. Although they are not present, they have--in the fullest sense of the word--a vital interest in the basic purposes of this Congress. For, as Thomas Jefferson wrote to a friend, "The art of life is the art of avoiding pain."

Thank you.

REMARKS*

by

James B. Wyngaarden, M.D.**

About two and a half years ago I was busily absorbing a large volume of data and information about the past and present of the National Institutes of Health. At the same time I was doing the necessary homework to understand the complexities of the current policy issues. All of this was to prepare me for the hearing to be held by the Senate to decide if I should be the Director.

My trusted guide through the minefields and quicksands of this and many other journeys to the Hill was Mike Goldberg. The briefing materials he gave me were always masterfully prepared. They contained a wealth of solid information, but were not cluttered with trivia. Whether written by Mike or members of his staff, those documents always reflected his special insights and his selection of the topics that were worthy of emphasis. His stamp of commitment and excellence has been apparent in the materials we have come to expect from Mike--especially in connection with the legislative scene, program evaluation, and the Director's Advisory Committee.

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*Farewell to Dr. Michael Goldberg, ADPPE, Wilson Hall, NIH, September 12, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

In the nature of things, an agency of this size needs--and generates--a cascade of background documents, analyses, and position papers. For the person who must read and think about the issues described in the papers, what a pleasure it is to find the prose lucid, spare, and thoughtful as it almost invariably turns out to be when produced by Mike and company.

Mike, we will miss your advice and the products of your skills, intelligence, and dedication, and we wish you the best as you continue what is already an outstanding career.

1984 G. Burroughs Mider Lecture

September 12, 1984

"Enhancers--Regulatory Elements in Eukaryotic Gene Expression"

by

Dr. George Khoury
Chief, Laboratory of Molecular Virology
National Cancer Institute (NCI)

INTRODUCTION (Dr. James B. Wyngaarden):

Dr. George Khoury received his undergraduate degree cum laude from Princeton University in 1965; his medical degree cum laude from Harvard Medical School in 1970. While at Harvard, Dr. Khoury worked with Nobelist Dr. John Enders and received his first training in virology. He was also introduced at this time to the monkey tumor virus SV40, which he has continued to work with in his studies.

He began his internship at Massachusetts General Hospital in 1970. Afterwards, in 1971, he joined us here at NIH in the National Institute of Allergy and Infectious Diseases (NIAID) as a research associate and scientist.

Dr. George Khoury is a pioneer in using viral vectors for research in the expression of eukaryotic genes. At NIAID, he initiated studies with Dr. Malcolm Martin on the transcriptional control mechanism of viral and eukaryotic gene expression.

Their team also developed the first transcriptional map of SV40. Later they were able to show that a subset of the SV40 genes, the early viral genes, was expressed in transformed and tumor cells.

Dr. Khoury joined the NCI in 1976, when he became the head of the virus tumor biology section of the Laboratory of Molecular Virology. In 1977 he was among the first to elucidate the post transcriptional control

mechanisms of RNA splicing, using SV40 as his model system. His studies there demonstrated, at the biochemical level, the evolutionary relationship of the human cancer viruses BK and JC.

In 1980, Dr. Khoury was named chief of the Laboratory of Molecular Virology. In collaboration with his colleague Dr. Gilbert Jay, Dr. Khoury initiated a series of experiments that have contributed to our understanding of histocompatability genes. Through their efforts to clone the mouse H-2 genes, they uncovered evidence for a new form of secreted H-2 molecule.

His recent interest in gene regulation has now given us some of our first views of the "enhancers" that regulate the activity of specific viral and cellular genes.

Dr. Khoury's career at NIH has given him worldwide recognition for his contributions to virology and oncology. Two of his distinguished awards for his work here at NCI are the Outstanding Young Maryland Scientist Award in 1977 and the Arthur S. Flemming award in 1981.

This evening Dr. Khoury will present the 1984 Mider lecture, "Enhancers--Regulatory Elements in Eucaryotic Gene Expression." It is my pleasure to introduce Dr. George Khoury.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20205
Office of Cancer Communications
(301) 496-6641

NOTE TO REPORTERS AND EDITORS:

Dr. George Khoury, chief of the Laboratory of Molecular Virology in the National Cancer Institute (NCI), will deliver the 1984 G. Burroughs Mider lecture, "Enhancers--Regulatory Elements in Eukaryotic Gene Expression." The lecture will be given at 8:15 p.m., Wednesday, September 12, in the Clinical Center's Jack Masur Auditorium at the National Institutes of Health (NIH). The public is invited.

The Mider Lecture was begun in 1968 to honor the distinguished service of Dr. G. B. Mider, a former director of Laboratories and Clinics for NIH. The lecture is awarded annually to a NIH scientist to recognize outstanding scientific contribution and to provide for an exchange of important research information.

Dr. Khoury will discuss his search for the cell mechanisms that selectively turn on and increase the activity of certain genes.

Although every cell in a human body has the same genes, each different cell type makes use of only a fraction of its genes, allowing the cell to produce specialized proteins, such as antibodies or hormones.

The quest for the mechanism that "turns on" specific genes in different cells led Dr. Khoury and his associates to the discovery of an "enhancer sequence" that is necessary for the expression of a certain gene in a monkey tumor virus (SV40). Later, Dr. Khoury and other scientists discovered similar enhancers in other viruses, including RNA tumor viruses.

(More)

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Because similar rules govern gene expression in both viruses and cells, researchers in many laboratories looked for and found enhancers in animal and human cells. Some of the enhancers they found turned on antibody genes in antibody-producing cells, others turned on insulin genes in insulin-producing cells.

Many cellular genes, however, do not have a strong enhancer to stimulate their activity. An infecting virus, with a stronger enhancer, may overpower the normal operation of a host cell. The infecting virus's oncogenes (cancer-causing genes) may thereby possibly transform a normal cell into a cancer cell.

Knowing what turns on certain genes to make a cell produce a certain protein, like an antibody, or to become a particular type of cell, like a blood cell, is critical to the use of gene therapy for treatment of a number of diseases. Discovering the mechanisms of enhancer operation can also help researchers better understand both normal and cancer cell growth.

Dr. Khoury has won two distinguished awards while working at NCI, the Outstanding Young Maryland Scientist Award in 1977 and the Arthur S. Flemming award in 1981. He belongs to many professional societies and serves on the editorial boards of the Journal of Virology and Cell.

A photograph of Dr. Khoury is available upon request.

# # #

Mailed August 24, 1984

This announcement was written by Steve Weiss, an intern in science writing in the Office of Cancer Communications.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

before the

COMMITTEE ON AGRICULTURE

SUBCOMMITTEE ON DEPARTMENT OPERATIONS, RESEARCH

AND FOREIGN AGRICULTURE

U.S. HOUSE OF REPRESENTATIVES

SEPTEMBER 19, 1984

Mr. Chairman and members of the Subcommittee, I am pleased to present to you this morning the views of the National Institutes of Health (NIH) on legislation concerning the care, treatment, and use of research animals and to describe to you some of the activities we have undertaken to address this issue. I am accompanied by Dr. William E. Raub, the NIH Deputy Director for Extramural Research and Training.

Let me begin by stating our general views on H.R. 5725. I think the bill reflects a good understanding of some of the fundamental concerns and needs of the biomedical research community. It seems to have been carefully crafted after a thorough review of the issues. In particular, we agree with its goal: namely, a system that provides for effective oversight of the use of animals in research; close involvement of institutional committees with the animal care and use programs of those institutions; training of administrators, scientists, and technicians in humane animal care; availability of information about potentially useful methods and models which might reduce the number of animals needed for research; and adequate and effective communication with the public about the use of animals in research. We do not agree, however, with the premise that new legislation is needed to achieve that end. I am convinced that under existing law and administrative authority we are working effectively in pursuit of goals I know we share with you, others in the Congress, and the public.

I want to acknowledge your efforts, Mr. Chairman, and those of your staff, in recognizing and attempting to take into consideration in drafting this bill some of the concerns of the Department of Health and Human Services (HHS),

NIH, and members of the research community. We believe that when animal welfare legislation reflects a clear understanding of the needs of research it is in everyone's best interests. We remain convinced that the physical and mental health and well-being of this Nation depend on biomedical research, and that the use of live animals in such research will continue to be imperative. We cannot foresee a time when this will not be the case.

At the end of last year, HHS submitted comments to the Senate Agriculture Committee expressing concern about Senate bill 657, which is similar in many respects to H.R. 5725. Two examples of differences between S. 657 and your bill reflect your understanding of those earlier HHS comments. One concern was the use of the term "methodology," a concept we believe is easily confused with the concept of protocol. Research protocols should be established and reviewed by scientists with expertise in the particular area of research in question. Your bill takes account of this concern both by using the term "practices" and by clarifying, appropriately, that the promulgation of regulations regarding experimental design is not authorized. Another concern was the ambiguous requirement for "adequate exercise" for all research animals. This would have created a problem relative to the establishment and enforcement of standards, since exercise requirements differ among species and with environmental conditions. Your bill limits this problem by confining the exercise requirement to dogs.

Turning to comments of a more general nature, Mr. Chairman, I would like to reiterate that there is already sufficient legislative and administrative authority to assure humane care and treatment and appropriate use of research animals. There is also sufficient authority for appropriate action when Federal awardees fail to observe laws, regulations, guidelines, principles, or policies. The Animal Welfare Act, administered by the Department of Agriculture (USDA), applies to research institutions. We believe that its current authority is satisfactory and allows the USDA to change procedures and standards as necessary. In addition, the Public Health Service (PHS) has used its authority to promulgate policies and guidelines relative to animal welfare for its own awardees. There is sufficient flexibility under that authority to modify this policy as needed.

To clarify this point a bit, I would like to describe briefly our current policies and procedures relative to awardee institutions where animals are used in research. Under current PHS policy, as a condition of a PHS award for research in which vertebrate animals are used, the awardee institution must provide written assurance that it has established an animal care committee to oversee care and welfare of animals used in research. Every institution for which we provide funds for vertebrate animal research in fact has such a committee, composed of a minimum of five members, at least one of whom is a veterinarian. Institutions provide us with the names and qualifications of the committee members, and are required to keep us informed when committee membership changes. Every institution using vertebrate animals in research

must include in its written assurance, which is kept on file with the NIH Office for Protection from Research Risks, a statement that the institution is committed to following the principles and guidelines of the NIH Guide for the Care and Use of Laboratory Animals (the Guide). About one-third of these institutions have sought and received accreditation from the American Association for Accreditation of Laboratory Animal Care (AAALAC), the best evidence, we believe, of full compliance with our Guide. The remaining institutions are either in full compliance with the Guide as determined by their animal care committees or are working toward compliance.

Let me just mention that our Guide is generally acknowledged as being a standard of animal care and treatment. It is updated periodically to reflect the "state of the art" in animal care. In fact, the Guide is now being revised, under contract from NIH, by the National Academy of Sciences Institute for Laboratory Animal Resources. The revision will be published next year.

In terms of compliance with our PHS animal welfare policy and with our Guide, as in other matters, NIH has relied on an assurance system. We believe that the most effective way to ensure proper laboratory animal care is to place responsibility squarely on the shoulders of researchers and officials at institutions where animals are being used. This must be a full-time concern, and only those at the institutions are there full-time. We have not felt the need to establish a system of routine inspections--a system which would in

many ways duplicate activities of other agencies, including the USDA, and for which we do not have the necessary resources. We know that the Congress and the public have not always shared our confidence in the effectiveness of our system. We are also aware that even one report of a violation causes criticism to increase. Because of our awareness of your concern and that of the public, and because we believe the public trust is important, we have initiated and participated in a number of activities designed to evaluate our assurance system; tighten our animal welfare policy; and enhance our communications with the public, with our awardees, and with other government agencies having similar responsibilities for animal care and treatment.

I would like to spend a few moments describing some of these activities, which I think illustrate that we have adequate legislative authority and are willing to take positive action which can benefit the animal subjects of research while preserving the integrity of the scientific process.

In the NIH intramural program, we recently issued a new directive on the care and use of laboratory animals. This document stipulates that each NIH Institute must have an animal research committee to advise the Institute's Scientific Director on the care and use of laboratory animals, review research proposals, and conduct animal care and handling training programs for investigators and technicians. The committee is composed of five members, including a veterinarian who actually attends the animals in that Institute and a nonscientist from outside the Institute.

In the spring of 1983, we participated with the Food and Drug Administration (FDA) and the USDA in the development of a Memorandum of Understanding designed to increase interagency communications with respect to deficiencies related to animal care and treatment. We recognized that previous communications had been inadequate, and that these agencies, with their inspection responsibilities, could be very helpful in calling attention to problems. We expect that communication will continue to improve because we, the FDA, and the USDA have a commitment to improve it. We know we must talk to each other and I assure you, Mr. Chairman, that we will continue to do so.

Over the summer of 1983, NIH site-visited a small sample of randomly selected awardee institutions. The purpose of these visits was not to evaluate every institution's animal program comprehensively but to assess the viability of our own assurance statement system. The visits were organized by the NIH Office of Extramural Research and Training and included members of intramural and extramural staffs and outside consultants, including veterinarians. There were two significant findings of the site visits: no abuses of animals were found, and our assurance statement system and our animal welfare policy were determined to be good but not perfect. As a result, we made several decisions.

First, we decided to continue a small program of random site visits. Indeed, another series of five was completed about three weeks ago. Again, these

visits are not to duplicate or replace the unannounced inspections of the USDA Animal and Plant Health Inspection Service (APHIS). They are designed to continue to emphasize to our awardees that their assurance statements are essential and must accurately reflect the status of the institutions' animal care and treatment programs. Through such site visits we will continue to assess the effectiveness of our assurance system and identify any problems which may develop with that system.

Second, we have proposed a revision of the PHS policy on animal welfare, strengthening the policy in accordance with suggestions of site visit team members and suggestions made to us through various means by the Congress and the concerned public. We published the proposed revision in a special edition of the NIH Guide for Grants and Contracts in April 1984, and solicited public comment both in writing and at three public hearings in Kansas City, Boston, and Seattle. We received over 300 comments from researchers, institutional officials, humane organizations, and individual citizens. We are currently analyzing those comments and will publish a final version of the revised policy after taking into account the views of all who commented. We expect this process to be completed by early next year.

Let me just highlight a few aspects of the proposed revision that relate particularly to H.R. 5725. Our proposal would require that institutional animal research committees (1) include a member not affiliated with the institution, and a nonscientist; and (2) be involved to some extent in the

review of proposed research protocols, with an objective being to determine that the care and use of the animals are in compliance with the Guide and other applicable regulations. I might mention, Mr. Chairman, that we have received a great deal of comment on this latter aspect of the proposed revision. As you might imagine, it was one of the more controversial aspects. The proposed revision would also require a more frequent updating of institutional assurance statements, and a specific timeframe for complying with the NIH Guide, for those institutions that do not have AAALAC accreditation.

Next, we embarked on an education campaign which began with a two-day National Symposium in April of this year and will include a series of regional workshops dealing with the PHS animal welfare policy, directed primarily to institutional animal research committees and research administrators; development of a guidebook for animal research committees; archiving of available audiovisual material related to humane research procedures, animal care and handling, etc., and development of new ones; and preparation of printed materials to increase public understanding of animal use in research.

Concern about animal welfare frequently leads to discussion of the extent to which the use of animals can be reduced. The NIH Division of Research Resources has funded a series of workshops, sponsored by the National Academy of Sciences, on the subject of what are sometimes termed "alternative" or

"adjunct" methods of research. The workshops, which were completed in late summer, brought together scientists from many disciplines, to discuss such topics as cell culture methods, mathematical/computer modeling, and the use of lower organisms in research. These workshops served to make many more scientists aware of various research methods and models that might now or in the future be available for particular kinds of research activities. It is expected that the forthcoming report of the National Academy of Sciences will include recommendations regarding the funding of research in the development of promising models and methods. NIH is funding such research and is ready to expand its efforts into promising new areas.

In closing, Mr. Chairman, I want to say that we are convinced that researchers, with rare exception, respect animals as unique and valuable resources, use them prudently, and do not abuse them. Further, we at NIH are committed to the humane care and treatment of research animals and to their appropriate, thoughtful, and careful use. The same commitment is expected from our awardee institutions.

Thank you.

I would be pleased to answer any questions you may have.

REMARKS*

by

James B. Wyngaarden**

The singularly appropriate action we are taking today is long overdue. If there is any person anywhere whose name should be prominently displayed on this campus, it is Mary Woodard Lasker.

She has advanced the cause of health immeasurably, and as a part of her deliberate strategy for doing so, she has been an indomitable champion of the National Institutes of Health. Throughout the history of the modern NIH, Mary Lasker's presence has been felt. Often her ideas and vigor have made the critical difference.

Other centers at NIH bear the names of John Fogarty, Lister Hill, and Warren Magnuson. But I think each of them would have agreed that a substantial share of the credit for their accomplishments on behalf of NIH belongs to Mary Lasker for her skillful and unrelenting efforts.

She has tutored Presidents, Senators, Congressmen, and other leaders in American life on the importance of health-related research and why it should be supported. Perhaps one of her most difficult tasks has been to teach scientists how to communicate with the real world. Her appreciation of what science can do is as

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*Mary Lasker Day at the NIH, September 19, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

profound as that of a scientist, but her ability to present the case for science outstrips us all.

Repeatedly she has shown the qualities of a master teacher as she has appeared before Congressional Committees, always fully prepared in sharply focused presentations. She has little patience for the negative or halfhearted and has been known to lecture program leaders, Institute Directors, Assistant Secretaries, and even members of the President's Cabinet when she felt that they needed it.

Her formal affiliation with NIH began when she was appointed to the first National Advisory Council of the Heart Institute; she was the first nonscientist, nonphysician Council member. In a moment, Dr. Lenfant will tell more of her role in the successful assault on heart disease, and Dr. DeVita of her leadership against cancer. Additionally, her interests and efforts in the fields of mental health, vision, neurological disorders, and arthritis had much to do with the establishment of Institutes to concentrate in those areas.

Her dedication to the cause of research has extended beyond the categorical and disease specific to emphasis on the importance of fundamental studies. She served a term as a member of the National Advisory General Medical Sciences Council. She has been a member of many different advisory bodies, most recently as a member of the Director's Advisory Committee, where during the past two years I have been privileged to see her in action. Invariably, she has identified the real issues and has forcefully addressed them. It has been especially interesting to me to observe the respect her

views about biomedical research command from leading scientists and educators who themselvs are inclined to have strong views about such matters.

My recent membership on the Albert Lasker Medical Awards Jury has given me opportunity to observe firsthand the fervor with which Mary Lasker regards medical research and her determination to settle for no less than the best.

As we near our one-hundredth anniversary, it is likely that our thoughts will be turning more often than usual to the people and events associated with the growth and accomplishments of the National Institutes of Health. As that record is examined in detail, it is inevitable that we will learn more and more of the unique and practically indispensable role played by Mary Lasker.

LECTURE*

by

JAMES B. WYNGAARDEN, M.D.**

At the outset, I will take this opportunity to express personally and on behalf of my colleagues at the National Institutes of Health heartiest congratulations to Dr. Robert J. North and the staff of the Trudeau Institute on attainment of this special anniversary. Please accept our best wishes for a second century of distinguished service to humanity.

A centennial is a subject of special interest to me just now, for we are planning for our observance of the 100th anniversary of the National Institutes of Health. We trace our origins to the Hygienic Laboratory set up in the Marine Hospital in 1887 on Staten Island for the study of cholera, yellow fever, and other infectious diseases.

In preparing for the centennial events, we have been delving into the early history of the Institution. It was fascinating to learn, for example, that in addition to their battles against disease, the founding scientists were engaged in a fierce bureaucratic struggle. The two principal contestants were our organizational ancestor, the Marine Hospital Service, and the then newly created National Board of Health. This decisive battle was joined over the construction of a refrigerator ship, but the basic issue was not supremacy of the seas but the more familiar contest for bureaucratic turf. As it turned out, this time of troubles became the birth pains of the National Institutes of Health.

The National Board of Health was created by the Congress in 1879. One of the Board's first moves was to ask for a tenfold increase of its own budget. It proposed to take from the Marine Hospital Service authority over the newly passed quarantine law which established a national framework for collaboration on health measures with states and cities. The legislation creating the new body called upon the Board to frame all rules and regulations to prevent the introduction of contagious diseases into the United States, to gather information on all matters affecting public health and give advice on the subject to the federal government and the states, and to prepare a plan with assistance of the National Academy of Sciences for a permanent national public health organization.

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*Lecture presented at the 24th Annual Meeting of the Association for Independent Research Institutes, Trudeau Institute, Saranac Lake, New York, September 21, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

The urgent attention given to this matter by the Congress reflected public alarm over the yellow fever epidemic of 1878. That fear provided powerful motivation for any action that appeared to have promise. Because yellow fever apparently came into this country on infected ships in the summer and died out with the coming of frost, the National Board of Health became convinced that a refrigerator ship could be used to treat incoming cargo as well as the clothing of crews and passengers, thus killing whatever it was that caused the disease. Within weeks, the Congress appropriated $200,000 to be used by the Secretary of the Treasury for the construction of the ship and provided that the plans were to be approved by the National Board of Health. The Marine Hospital Service chiefs were not particularly charmed with the project or, for that matter, with any of the threatening activities of the Board. In a short time, however, the Board's plans for the refrigerator ship were completed and submitted to the Secretary of the Treasury.

But the Secretary of the Treasury referred the Board's plans to his principal health advisor who was also the supervisory Surgeon General of the Marine Hospital Service, Dr. John B. Hamilton. To make a long story short, the plans for the ship sank slowly from sight under the waves of paper whipped up by strict interpretation of the procurement regulations as applied by the Secretary with the advice of the Surgeon General.

The battle raged on, however, for almost a decade. One last full-scale attack was made on the Marine Hospital Service in early 1888. Friends of the now defunct National Board of Health had successfully lobbied committee approval of a bill to set up a Bureau of Health in the Department of the Interior. The proposed legislation would have stripped from the Marine Hospital Service all of its public health functions but quarantine. In her book, "A Profile of the United States Public Health Service," Bess Furman tells how, even after the committee had voted to report favorably on the bill, Surgeon General Hamilton appeared at his own request on February 24, 1888, to oppose the measure. He testified that the Marine Hospital Service was already doing all that the proposed Bureau of Health would be authorized to do.

"But how about research?" the Committee asked.

And Hamilton played his trump card which, Ms. Furman said, "probably saved his Service."

The Surgeon General's ace was his testimony that the Service had already begun to conduct medical research in a small laboratory on Staten Island--and that several hundred dollars had been spent in

setting up the laboratory. He revealed that, only a few weeks before, research reports had been published on the work being carried out in the laboratory by an officer in the Service, Dr. Joseph J. Kinyoun, who was named as head of the research facility.

This was the first time a committee of Congress had heard of the National Laboratory of Hygiene which eventually would become the National Institutes of Health.

At that time, medical science in the United States lagged far behind that in Europe. The new discipline, bacteriology, led by Pasteur and Koch, was involving more and more European laboratory workers, but few Americans had participated in that advance. The new National Laboratory of Hygiene was in effect a fragile transplant from Europe, for Dr. Kinyoun had studied with Koch as well as at the Pasteur Institute in Paris. The tiny research center on Staten Island was founded on the work of Pasteur and Koch.

In much the same way and at about the same time, Dr. Edward L. Trudeau was putting into beneficial use here at Saranac Lake the new insights gained by the great European investigators.

For the first 50 years of its history, the NIH continued as essentially an independent, freestanding laboratory of limited size. The Nation's response to the challenges of World War II brought about the formation of productive partnerships involving the government with both academic institutions and independent laboratories for the conduct of biomedical research. In response to the sudden need for additional knowledge on how to deal with the health problems of the armed forces, the military had little choice but to turn to established nonfederal laboratories for the conduct of vital studies. By grants and contracts, most American scientists not in the federal service were mobilized for support of the war effort. The arrangement worked. It worked extremely well. The new partnerships greatly accelerated biomedical research and development across the spectrum from the most basic studies to the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

Perhaps the most dramatic statement of the effect of such improvements in medicine is a comparison of the death rates of service personnel during World War I and World War II.

Remarkable changes took place in just one generation. The death rate for all diseases in the army, including overseas forces, declined from 14.1 to .6 per thousand, almost a twenty-fivefold reduction. Dysentery, formerly the scourge of armies, became a minor problem.

Tetanus, typhoid, paratyphoid, cholera and smallpox were practically eliminated. As a result of the development of a potent vaccine and mosquito control, yellow fever did not appear in the army or navy in World War II.

But the modern era of biomedical research really began when the federal government and America's academic and other scientific research laboratories formed the wartime partnership for the purpose of carrying out such research. As is the case in any enduring relationship, both parties have continued to be well served by it.

The federal government's principal arm for biomedical research, the National Institutes of Health, has been the source of increasing amounts of funding for the support for biomedical research. The money has been made available mostly in the form of grants awarded competitively. Thus, the Nation's institutions have found a reasonably stable source of funding for their biomedical research programs and at the same time the NIH has gained access to the creative ideas of essentially the Nation's entire research community.

These extramural activities quickly became the primary mode of operation of the rapidly growing agency and their dominance has persisted. In recent years, 80 percent of our total budget has been used for the support of extramural research through project grants, training grants, and contract awards.

Outside groups, voluntary health organizations, and professional scientific societies had much to do with the establishment of the categorical institutes that formed the NIH. In listing influential individuals and groups, the first that come to mind are Mary Lasker and her colleagues. Mrs. Lasker has dedicated her abundant energies and formidable skills to the improvement of health through the extension of research. Just two days ago, we celebrated Mary Lasker Day at NIH as we carried out the congressional action naming a newly acquired facility there, the "Mary Woodard Lasker Center for Health Research and Education."

The so-called "Lasker Lobby," as well as other important groups, has had much to do with the growth and development of the NIH. In his book on "National Priorities for Health," Robert F. Rushmer commented, "The lobbyists insisted on bold and expansive approaches to the problems of health. The Congress as a whole was generally more cautious but was still more daring than the scientists and medical community who consistently displayed a conservative attitude about targeted research.

"The net result of these countervailing forces was an accelerating rate of growth that was stimulated by lay public, modulated by Congress, and accepted with increasing enthusiasm by the biomedical research community. The objectives of research were identified on the basis of categories which had broad public appeal rather than a solid base of scientific knowledge from which to launch an attack. The intent of Congress was to support research that would contribute rather directly to improved diagnosis, management, cure, or prevention of the various diseases under attack. Dr. James Shannon (who was Director of NIH at the time) was able to persuade Congress that a large-scale development of basic medical sciences was an essential step toward the ultimate goal of cutting or controlling pathological processes. The result has been a broad scale frontal attack on selected disease categories with simultaneous scientific intrusions from the most fundmental to the most applied research and development. The successive additions of categorical institutes of health have represented the principal thrust of the effort."

But many of the "outside" groups and individuals who strongly advocated new categorical initiatives, and in some cases new institutes, were also effective in supporting budget increases for the agency. The extremely rapid growth of the NIH from the mid-fifties to the late sixties was unique. A number of fortuitous circumstances contributed to the virtual explosion in funding. The conjunction of the influence of strong leaders like Shannon, Fogarty, Hill, Lasker, and others of like conviction would have been a powerful force for any cause, and when linked to a growing national confidence in science, it became irresistible.

It was obvious, of course, that the year-to-year budget increases of 25 percent could not continue. By 1969, the budget curve began to flatten noticeably and for more than 10 years the annual increases barely offset inflation. In constant dollars, the NIH appropriation was essentially unchanged for the decade beginning in 1970 or 1971. But as compared with a number of domestic programs, the NIH has fared relatively well in a time of budget stringency.

Much of the credit for NIH's relatively favorable budget treatment is owed to the cooperative efforts of a number of societies and organizations having various interests in biomedical research. One of these groups, the "Delegation for Basic Research," has been especially effective in its efforts to present to the Congress and the Administration the need for emphasis on fundamental studies as prerequisite to success in most disease-oriented research. Mahlon Hoagland, Brady Metheney, Federico Welsch and their delegation colleagues have had an important impact on the federal biomedical research enterprise.

In connection with the FY 1985 budget, the "Ad Hoc Group for Medical Research Funding" proved to be highly influential through careful preparation and presentation of an alternative budget proposal for the NIH. As it turned out, appropriations committees of both Houses accepted in large measure the group's budget recommendations. The large and diverse Ad Hoc Group united their efforts out of concern for the vitality of the medical research enterprise as a whole, while submerging their individual agendas.

It is appropriate to note that this consolidation of efforts by divergent groups is mirrored in the nature of contemporary science where convergence is the order of the day. Permit me to offer a few examples of progress that has resulted from the successful mix of disease-oriented, targeted research and fundamental studies.

Advances in the treatment of cancer have been remarkable. Based on scientific knowledge accumulated over several decades, therapy for cancer has improved to the point where we may have passed the 50 percent curable mark. Some of the cancers with the most encouraging five-year relative survival rates are: thyroid, 92 percent; endometrium, 87 percent; testis, 82 percent; melanoma, 79 percent; female breast cancer, 73 percent; and Hodgkin's disease, 70 percent. Much of this increased survival is due to improved therapy through chemotherapy, surgery, and radiation, sometimes in combination. And there are other advances on the horizon: Scientist-physicians are attempting to sensitize tumors to make them more susceptible to the effects of radiotherapy; investigators at several locations are studying the benefits of applying radiotherapy <u>during</u> surgery to avoid toxicity to normal tissues; and still other scientists are working to apply the new monoclonal antibodies and interferons to detect and destroy cancer cells.

Recently, there have been a number of important advances in kidney disease research: Kidney stones that once would have required surgery now can be pulverized using a new, noninvasive shock-wave treatment known as extracorporeal shock-wave lithotripsy. Other research has shown that the drug potassium citrate inhibits the formation of kidney stones associated with low levels of urinary citrate, thus effectively preventing future stone formation in certain patients.

Concentrated effort on vaccine development has yielded positive results: Scientists have combined vaccinia virus with genetic material from hepatitis B virus, producing the first of a new generation of live, recombinant vaccines. The technique has also been used to combine vaccinia virus with genetic material from influenza

virus, from rabies virus, and from genital herpes virus. In the future, a single recombinant vaccine might protect individuals against many diseases.

Just about a month ago, it was announced that scientists at NIH, collaborating with others, had moved science closer to development of an effective malaria vaccine. They had learned, by using genetic engineering techniques, to cut intact genes--DNA segments--directly out of the genome of the malaria parasite. Their success in cloning the gene for the complete major antigen of one form of the malaria parasite opens the door to large-scale synthesis of the antigen, which in turn could be tried as a vaccine.

We have seen major advances in some of the genetic diseases: The work going on now in the Lesch-Nyhan syndrome is just an example of what is to follow in other areas. Scientists have recently cloned the gene for HGPRT--the enzyme missing in Lesch-Nyhan--and have been able to insert it into defective cells in vitro and in mice in vivo, with success in correcting the deficient function. The Lesch-Nyhan syndrome may be the first candidate for gene therapy in humans, with other similar genetic metabolic diseases to follow.

In another genetic disorder, Huntington's disease, scientists have recently mapped the defective gene to the short arm of human chromosome 4. As a result, the prospects for an early diagnostic test are very good. Of course, as is true with many medical advances, especially when predictive tests for genetic and infectious diseases are developed, societal and ethical questions often come to the forefront.

As a result of many years of clinical and basic investigation, respiratory distress syndrome (RDS)--a life-threatening lung disease--may now be largely preventable in premature infants. A recent clinical trial has shown that the administration of steroids to pregnant women shortly before premature delivery is safe for both mother and infant and is extremely effective in reducing the incidence of RDS in female infants. The study also unexpectedly showed that all of the infants of mothers so treated had a threefold reduction in a serious intestinal disorder of newborns.

Several research investigations have suggested the possibility that direct replacement of alpha-1-antitrypsin (AAT) may be beneficial for the estimated 30,000 people in the U.S. who are likely to develop emphysema because of a genetic deficiency of that enzyme. Genetic engineering technology has played a role in these investigations, for a genetically engineered version of AAT will soon be tested clinically.

Major inroads have been made against eye disorders: For example, a recent collaborative study has shown that treatment with Argon laser beam can dramatically reduce the risk of visual loss from one type of senile macular degeneration. It is estimated that appropriate application of the study results could prevent severe visual impairment in an estimated 70,000 Americans a year.

Nearly everyone has heard of the co-discovery--by NIH scientist Dr. Robert Gallo--of the etiologic agent in Acquired Immune Deficiency Syndrome (AIDS); that is, the retrovirus HTLV-III. This major discovery and related studies producing large quantities of the antibody to the HTLV-III are the basis for development of an assay to screen donated blood for antibodies to the agent, thus assuring a safe blood supply. The discoveries have further significance in that HTLV-III may be the first human retrovirus for which an effective vaccine may be produced.

To mention one final advance: Scientists supported by the NIH have recently uncovered one key to the mechanisms underlying Alzheimer's disease. In autopsy studies, investigators found that in Alzheimer's disease brain tissue has a less than normal amount of RNA due to uninhibited activity of ribonuclease and a corresponding decrease in protein synthesis. This work has been corroborated by others in living tissues. French scientists have found, by using PET scanning, that there is a dramatic drop in brain protein synthesis in patients in the later stages of Alzheimer's disease. Such studies bring us ever closer to finding out what causes this debilitating illness.

I have talked a great deal about research advances that are fully entrenched or now entering the clinical arena, but we should remember that all of those advances are based upon fundamental research of earlier years. The basic research going on now in laboratories all across the country--for example, on oncogenes (the likely switches that make normal cells into cancerous cells); on the molecular events permitting cancer metastasis; on the chemical basis of drug resistance; and on the basic mechanisms of tissue contractility, particularly as it relates to skeletal muscle and vascular and cardiac muscle--is now laying the framework for the clinical applications of the future.

This kind of progress in the application of science to health has stimulated expectations. People today are being taught to expect good health care. In the past, throughout history, illness, plagues, and personal injury were accepted as normal events. This is no longer the case. The ability of medicine to control or eradicate

disease--mostly a legacy of modern research--has brought into being new hopes and even demands. Inevitably, such a development has major economic implications.

A five-year study attempting to quantify the worth of biomedical research was conducted in the late seventies. The results were published in 1979 in a book by Selma J. Mushkin, titled "Biomedical Research: Costs and Benefits." The study addressed the question, "Is the public getting an appropriate return for the multibillion dollar yearly expenditure on health research?"

The answer was an emphatic "yes," when the yardstick included actuarial estimates of the dollar value of the productivity of the lives saved and the years of sickness averted. For the 75-year period beginning in 1900, the ratio of total cumulative benefits to total research and development costs was about 13 to 1. In more recent years since 1930, the ratio was 5 to 1. The recent somewhat lower but substantial return reflects the cost of the large amount of basic research conducted during the past 40 years. The payoff from such research is certain to affect strongly and favorably the future ratios of benefits to costs. Current expenditures for basic research are long-range investments.

In just one area, recent events have highlighted other beneficial and tangible effects of the national expenditures for biomedical research. For example, in the past seven or eight years, a totally new industry has emerged from the employment of the recombinant DNA, cell fusion, and related technologies. Incidentally, these new procedures and technologies were developed with public funds. In just one year, 1983, a billion dollars was invested by the private sector for the commercialization of the products of these new discoveries.

In the context of these economic benefits, we encounter a paradox; namely, that a substantial number of medicine's discoveries in recent years have increased rather than decreased the cost of medical care. This is an aspect of the economics of research about which there has been considerable public discussion of late. Heart and liver transplants and expensive futuristic diagnostic techniques could lead to vast additional health expenditures over the next generation.

When considering this question, however, we must not forget that each of these innovations represents for the patients involved and their families supremely important progress, hope, and benefits that cannot be measured.

Last summer during a press conference in a discussion of the rapid increase in the cost of medical care, I speculated facetiously that someone will someday suggest to the Office of Management and Budget that the best way to control health-care costs is to shut down the NIH. This was reported in the Los Angeles Times. About two weeks later, I received a letter from Harry Schwartz, long with the New York Times and now a writer and lecturer on medical issues. He reminded me that my prediction had been fulfilled before I made it--that he had been the someone who would suggest shutting down research to save on the cost of medical care. He sent me a copy of his article that appeared in the Wall Street Journal, April 3. "Do we really want medical progress," the article began, "or should we start thinking seriously of closing the National Institutes of Health and other public and private facilities now doing research to cure diseases and prolong lives?"

In his letter to me, he repeated what he calls Schwartz's first law of medical economics that reads, "In health care, the ultimate economy is death."

In the face of all this, I remain an optimist and believe that if we persist, one by one, these expensive halfway technologies that are now lifesaving will be rendered as obsolete as the iron lung, and will be replaced by simple, inexpensive and effective measures. But we must continue to search.

Most of us occupy positions of leadership in research institutions. We are responsible for assuring that our scientific colleagues have the kinds of support they need. We also must look to the future of the institutions we serve, as well as to the future of the research enterprise as a whole.

At the National Institutes of Health, for example, we are thinking seriously of possible ways for improving the processes by which applications for funds are made and reviewed. Can we maintain the integrity of peer review and yet require less specificity in grant applications? Can we lengthen the average term of first-time grants so that new principal investigators will not find it necessary to make application for renewal of their grant when it is 18 months old or less? For obvious reasons, we feel that first-time investigators are a highly important category of researcher who must be adequately supported. At the other end of the grantee spectrum is the outstanding and established investigator for whom a mechanism is needed for providing longer term, more flexible support. These and other questions related to grant mechanisms are under discussion at the NIH, and will become the principal item on the agenda of the next meeting of the Director's Advisory Committee.

Another matter requiring attention is the need to replace the old and acquire the new increasingly sophisticated instruments needed for today's research. It is estimated that 20 million dollars a year for five years is needed for the purchase of large-scale shared instrumentation resources, with additional funds for the purchase through research grants of the smaller instruments. The NIH is participating in a study by the National Science Foundation to secure a valid current assessment of national need.

Finally, extramural laboratories and facilities are slowly deteriorating. With the exception of funds from the Cancer Program and recently from the National Eye Institute, NIH has not supported the construction of facilities since 1969 and now lacks the legal authority to do so. As a result, many of the facilities built in part from the major NIH construction effort--the Health Research Facilities Program--are more than 20 years old or are rapidly approaching that mark. We believe that a realistic aim of any new federal construction program should be less ambitious, perhaps, than the previous one. It should, however, include new construction to replace outmoded facilities, to relieve overcrowding, to accommodate changing research requirements, including facilities for toxic wastes, for laboratory animals, and for major renovation and repair. Good information on construction needs is sparse, and a current study similar to that being conducted on instrumentation deficits is seriously needed.

As important as buildings and adequate instrumentation may be, there is another consideration of even greater moment. That subject is research training. In our view, the training and research programs are so closely interwoven as to be practically indivisible. Fortunately, the supply of Ph.D. scientists has held up very well, but the intense competition for research support has increasingly taken its toll of the amateur or undertrained investigator. The professionalization of research activity has progressively selected against the M.D. scientist who 15 years ago had a much better prospect of success in research applications than the Ph.D. applicant.

Concurrently, there has been a decrease in the number of physicians who are seeking research training. The application of scientific advances to maintain good health and to prevent and treat disease is ultimately the responsibility of the physician. The trained clinical investigator is the critical link between the laboratory and the health-care provider. In the face of the explosive growth of basic knowledge in the biomedical sciences which has opened up vast opportunities for clinical research, the shortfall in training of clinical investigators assumes additional significance.

In this connection, we were immensely pleased to announce in mid-August that the Howard Hughes Medical Institute and the National Institutes of Health are launching a substantial cooperative program to help increase the vigor of American biomedical research and to increase the flow of M.D.s into research careers.

Under the program, about 30 medical students each year will be chosen competitively from the Nation's medical schools. The selected students, after their second year in medical school, will receive from six months to a year of research training on the NIH campus in Bethesda in the laboratories of some of our finest scientists. The Hughes Institute will provide stipends, travel, and miscellaneous support for the students and will fund building renovation and construction for residential quarters, classrooms and teaching laboratories. The Hughes support for the total program is expected to amount to about 10.5 million for the first five years.

Recruitment will begin this fall, and the first group of students will enter the program in the fall of 1985. The quarters and classrooms for the Hughes Research Scholars will be located on the newly acquired Convent property within the NIH campus that was recently designated by the Congress as the Mary Woodard Lasker Center for Health Research and Education.

This new program brings together major elements involved in the NIH's research programs and brings to mind aspects of its history. Here we have a large independent research institute, working with the intramural research programs of the NIH, in offering to selected medical students a superb training opportunity. It is our conviction that this program can be of direct benefit in adding to the cadre of physician investigators and, perhaps more significantly, it will be influential as a demonstration of the value of such a training experience.

It is a special pleasure for me to meet with the members of this organization. It gives me opportunity to see a number of old friends and to express to all of you the appreciation my NIH associates and I feel for the steadfast support you have given us. We have many interests, satisfactions, problems, and possibilities in common. And we share the excitement of this time that is like no other period in the history of the biosciences.

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LECTURE*

by

JAMES B. WYNGAARDEN, M.D.**

Last Friday, I attended and participated in the annual meeting of the Association of Independent Research Institutes. The session was held at Saranac Lake, New York, where the host organization--the Trudeau Institute--was established in 1884. The meeting was held there as a part of Trudeau's centennial observance. Such anniversaries are of special interest to me just now because we will soon be celebrating the one hundredth birthday of the National Institutes of Health. As you may know, we trace our origins to the one-room Laboratory of Hygiene, set up at the Marine Hospital on Staten Island in 1887.

For the first 50 years of its history, the NIH was essentially a freestanding, independent laboratory of limited size. Only after World War II did the agency begin growing at the spectacular rate that multiplied the prewar appropriation of less than half a million by a factor of almost 10^4 to the current annual appropriation of $4.5 billion.

This growth would not have happened nor is to likely that it could have been possible if another and even more significant change

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**Director, National Institutes of Health, Bethesda, MD.

had not taken place. I am speaking of the formation of a partnership between the government and academic institutions for the conduct of biomedical research. It was a product of necessity. In responding to the sudden wartime needs for research on the health problems of the armed forces, the military had little choice but to turn to the established academic laboratories for the conduct of vital studies. By grants and contracts, academic scientists were in effect mobilized for the support of the war effort. The arrangement worked. It worked extremely well. While the fruit of prior basic research contributed greatly to wartime efforts, the new partnership greatly accelerated biomedical research and development across the spectrum from the most basic studies to the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

In 1945 with demobilization, the ongoing contracts and grants for biomedical research being conducted at academic and other nonfederal laboratories were transferred to the NIH for administration. These projects formed the nucleus of an extremely important new dimension for NIH activities; that is, the sponsorship of research conducted in academic institutions by nonfederal scientists. These extramural activities quickly became the primary mode of operation of the rapidly growing agency. In recent years, 80 percent of our total budget has been used for the support of extramural research through project grants, training grants, and contract awards.

For the past decade, about three-fourths of all NIH awards have been made to universities and other academic institutions. Currently, a little over one-half of all our grants and contracts are awarded for research and research training carried out by members of medical school faculties.

Concurrently with the development of this government-medical school partnership, there has been amassed an incredible store of biological knowledge, not to mention tremendous advances directly relevant to human health. The work recognized by the Nobel prize awards for the years 1958, 1959, 1962, 1965, 1968 and 1969--most of them recognizing work done in earlier years--can be said to have ushered in the age of molecular biology. That the era was in large part spawned by the government/academic partnership is evidenced by the fact that of the 17 individuals honored for these seminal discoveries in basic genetics, 12 were Americans, the majority was supported by the NIH. The major stimulas for this type of research, of course, was the proposal in 1952 by Watson and Crick of the "double helical" structure of DNA, which offered suggestions about the mechanisms of mutation and replication. The actual discoveries of the other Nobelists of the genetic research coterie were important, but of even more consequence was the epoch they engendered with their research tools and methodology. The succession of germinal advances in molecular biology resulted primarily from application of a

reductionist approach--their use of very simple systems--bacteria (especially E. coli) and viruses (especially bacteriophage) as the basis for their studies.

Much of the recent fundamental information gained in the biological sciences has been obtained by the process of reductionism--the exploring of details, and the details of details, until all the smallest bits of the structure, or the smallest parts of the mechanism are exposed to scrutiny. Many of the most exciting observations of molecular biology have been made in microorganisms. Similar techniques are being applied with increasing success in the isolation and characterization of eukaryotic cells in tissue culture. These studies have thrown new light on biologic mechanisms, particularly mechanisms of control of biosynthetic and degradative processes.

The scientists responsible for our evolving understanding of biologic systems know that the reductionist approach must often precede reconstitutive endeavors. Scientific progress rests on myriads of small observations, tedious measurements, and the findings of investigators asking humble, answerable questions. Instead of reaching for the whole truth, the scientist examines small, defined and clearly separable phenomena.

The reductionist approach has had a profound effect upon research that is not frequently perceived--it has blurred the lines between the

once sancrosanct territories of the biomedical disciplines. There has been a coalesence in language and in the techniques and methodologies of biochemistry, genetics, virology, microbiology, physiology and even anatomy, with the common language being that of chemistry. The knowledge gained in the area encompassed by the term molecular biology has expanded so greatly during the past 30 years that some say it is beginning to disappear as a separate entity, reduced to chemistry on one level and expanded into cell biology on another.

We may no longer know what to call these new scientists--molecular geneticists, molecular biologists, biochemists, or virologists--but it is clear that there is ample scientific opportunity for them to expand their spheres of interest. The era of science heralded by the discoveries in genetics in the 1950's and 1960's has provided the broad field of biology with a set of unifying principles and properties that can be tested in almost infinite variety.

Watson and Crick's hypothesis for the organization of DNA could be said to be akin to the theory of relativity in physics. In the biological realm, it might be said that not since Harvey's description of blood circulation has such a scientific stimulus been provided. Suddenly, questions which earlier seemed unapproachable were reconsidered, and new questions--not even askable before--could be posed. Now, thanks to that stimulus, to the availability of research tools

and methodologies, and to a cadre of scientists capable enough and flexible enough to take up the challenge, we know much about how genes are replicated enzymatically; how they maintain extraordinary fidelity, but occasionally mutate; how they are transcribed into RNA and are expressed as protein sequences; and how they expand in number as more complex organisms evolve.

This biological revolution is far from over, and in fact is beginning to approach major questions with immediate relevance to human health. The burgeoning work in oncogenes, for example, is drawing us closer to an understanding of how carcinogens, cocarcinogens and host factors may affect genetic apparatus in causing all types of cancers. The remarkable explosion in knowledge about globin gene structure and function provided by molecular biological-recombinant DNA technology has offered a unique opportunity to understand disease mechanisms and to develop novel approaches to therapy. Extension of the techniques of molecular cloning, restriction endonuclease mapping, and DNA sequencing promises the solution to both molecular mechanism and prenatal diagnosis of many genetic diseases. Recently, for example, restriction endonuclease mapping combined with cloned DNA fragments has been used to devise a strategy for recognizing carriers of Huntington's disease.

Because many of the understandings gained from the age of molecular biology are now beginning to move toward clinical application, it is obvious that we will need a healthy supply of physician/scientists to help in the "technology transfer" phase of research.

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This is a most exciting type of research, requiring someone who is both medically knowledgeable and scientifically trained.

But, given the rapid pace of advancement in research, the task of overtaking that advance and keeping abreast of it is growing more and more difficult for clinicians. Science has become complex, the methods intricate, and the required training long. The burgeoning of biomedical knowledge in the past decade has forced the progressive professionalization of biomedical research, in particular clinical research. I hope there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training in the information, concepts, and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

The importance of more and better quality training for our future physician/scientists cannot be overemphasized. Recent analysis by NIH has indicated that for M.D. postdoctoral trainees, the longer they have trained, the more likely they are to apply for and receive an NIH research grant; unless they have a minimum of three years of research training, they usually are not successful in competing for grants. The most successful applicants of all are those with combined M.D./Ph.D. degrees. Their success rates are higher than of those with

the Ph.D. degree and much higher than of those with the M.D. degree, chiefly, I believe because of inadequate research training. For example, we have found that in programs where the median length of training is only 12 months, only 20 percent of the M.D. graduates apply for grants and only 10 percent are successful.

There is a great deal of interest in this country--expressed by the Administration, by the Congress, and by the scientific community in finding means to provide for future clinical investigators. For its part, the NIH has an array of training and career development programs that are especially designed with M.D.'s in mind. Because we are convinced that early exposure to research is an important factor in attracting bright and dedicated students into biomedical research, we have set up a number of programs whereby students can supplement their medical education with research experience. For young physicians who are willing to make a major commitment to research, we have developed a new program--the physician/scientist program--which provides five years of support, including three years of training in basic research and an additional two years in a clinical setting.

Another new program, a cooperative effort of NIH and the Howard Hughes Medical Institute (HHMI), will offer approximately 30 medical students a year opportunity to try research after their 2nd year in medical school. They will be chosen competitively from the Nation's medical schools to spend six months to one year of research training

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on the NIH campus under the guidance of leading NIH scientists. HHMI will support this program at a cost of about $10.5 million for the first five years, to include stipends, travel and miscellaneous support for the students, and for building renovation and construction for residential quarters, classrooms and teaching laboratories. Recruitment will begin this fall with the first group of students entering the program in the fall of 1985. Although these two programs are just beginning, it is expected that early exposure to the excitement and intellectual challenge of research will encourage more medical students to undertake careers in biomedical research and that the programs will help to ensure a supply of physician investigators to participate in the "new scientific era."

The importance of scientific training to the small proportion of medical students who will make careers of research is obvious, but what about the vast majority who will practice medicine?

Since medicine is derived from a number of sciences relevant to the health of individuals or of groups, physicians must be scientists to utilize these complex disciplines effectively. To be a scientist, the physician must have more than rote scientific knowledge, or even fluency in its particular jargon. Physicians must be conversant with the processes of scientific inquiry--how data are obtained and evaluated; how hypotheses are framed, modified, or discarded; the uses and limitations of inductive reasoning. In short, they must understand

science as an intellectual instrument which has been slowly perfected over centuries. Only in this way can they remain attentive to medical progress as a critical and independent participant. Otherwise they will be in danger of being the passive purveyor of medical fashions. Both the spirit and rigor of science are necessary for the physician to become and remain a scholar in medicine.

It goes without saying that the state of scientific knowledge at any given time should be one of the factors shaping medical education. Although this has not always been the case, the content of the curriculum of most schools today reflects a reasonably successful attempt to keep up with the times. Because so much is now known about so many subjects of concern to the physician in training, there is an understandable tendency to add to the volume of material that medical students are required to have learned. The result can be an increasingly rigid and demanding curriculum.

To avoid this extreme, some faculties have conducted an agonizing reappraisal of curricular sacred cows; have accepted the view that everything important about everything important cannot be taught in four years; and require that their students make the kinds of choices in their predoctoral training that traditionally have been made by residents. About one thing we can be certain--namely, that medical education will continue to change.

Certainly academic medicine is not justified in adopting the attitude expressed by the lady from an old New England family. She lived in Boston and, according to Daniel Boorstin, when asked why she never traveled, replied "Why should I? I'm already there."

Over the years, factors other than the state of knowledge have had a strong influence on the structure and operations of medical schools and at times have influenced what is taught and how it is taught. It is no revelation, for example, to point out the effect that sources of funding have had on academic institutions--medical schools, in particular.

Some of the deep-seated problems attacked by the Flexnerian reforms in medical education resulted from financing proprietary medical schools from tuitions alone. There was a strong incentive for admission standards and graduation requirements to be tempered to fit the academic qualifications of as many applicants as presented themselves, provided of course they could meet the financial qualifications. Even so, proprietary schools faced steady increases in costs of medical instruction, and eventually they recognized the impossibility of meeting expenses from student fees alone. Since they were "for-profit" business ventures, these schools could not acquire endowments.

Some medical historians have argued that the medical schools of the early twentieth century sought affiliation with academic institutions because of financial problems and that Flexner's enduring legacy should derive from the funds he was able to direct into academic medicine from the General Education Board.

Medical educators have also felt the understandable pressures that arise from taxpayers' support. In most instances, states provide academic institutions to assure educational opportunities for their own young people and do not place unusual emphasis upon the output of its schools. In the case of medical education, however, the prime purpose in many states has been to increase the supply of physicians in the state. The accent has been on operating the medical school as a kind of utility for the state rather than as an educational opportunity for its people.

A new shaping force affected medical education with the emergence of the extramural programs of the National Institutes of Health.

When in the late forties it became apparent that federal support of research in academic institutions would be likely to continue and to grow rapidly, there were many in academic circles who were concerned. They worried about the possible effect of this new variable on the stability of the educational equation.

In the report on "Medical Schools in the United States at Mid-Century," John Deitrick and Robert Berson wrote, "The effect on both the university and the medical school of the support of research through project grants extends far beyond the question of finances. Such methods of support inevitably lead to direction of research by agencies outside the medical school and result in regimentation of the faculty and loss of freedom to follow their bent and their own clues to new knowledge. In carrying out project research, the investigator's freedom to pursue paths is inhibited. He is investigating 'to order,' as it were."[1]

In addition to the fear that project research might inhibit freedom of inquiry, there was concern that involvement of academic institutions in federally funded studies might lead to isolation of the research from the instructional programs. Educators were also concerned that existing differences in the strengths of the various departments of medical schools would be accentuated by federal support. They predicted that the already strong departments would attract a lion's share of federal support and the weak department would grow relatively weaker.

A more general reservation was expressed by the authors of the "Mid-Century" report in their discussion of trends in the financial support of medical school activities. They noted that "Research . . . receives greater emphasis judged by the increasingly larger sums

flowing to it from the public and being expended upon it than any other activity of the medical schools. If this trend continues, it will create a serious imbalance in the activities of the schools."[2]

During the fifties, there was also a growing concern among medical educators that the broad use of project grants for research support undermined the central authority of academic institutions and created instability. There was strong support in many quarters for the development of some form of institutional support for research that would return to the institution as such some measure of scientific initiative that would have a stabilizing effect on institutional finances. In 1960, Congress passed legislation authorizing an institutional research support instrument, the General Research Support Grant, whose amount would be determined by formula and would be proportional to the federally sponsored research being carried out by the awardee institution.

The General Research Support Program was hampered from the start by reservations among some members of Congress who felt that the obvious financial needs of medical schools should be addressed directly--not as an indirect object of research support. Opposition from the scientific community was also strong, reflecting the view of individual faculty members that they would rather have their application for funds judged by a national peer review group than have it decided upon within their own institutions. Deans, of course, took a different view.

Some years later, direct federal subsidies for operating medical schools were made in the form of capitation grants. Their purpose was to encourage medical schools to increase the numbers of students enrolled. They succeeded in doing so. In recent years, capitation programs have largely been discontinued.

A new shaping force affecting medical schools began to be a major influence in the sixties. I am speaking of faculty practice plans under which income from patient care by members of the clinical faculty became a source of financial support for the medical school. The AAMC reported that in the 1960-61 school year, six percent of all medical school income came from fees for medical services. This, incidentally, was about the same as the income from student tuition. In 1960 income from federal research grants and contracts was the largest source of medical school income--representing 31 percent of the total. By last year, however, the situation was much different. During the 1982-83 school year, more than 32 percent of medical school income came from medical services and 20.2 percent from federal research funds.

One other variable has entered the medical school financial equation in the past decade. It is what a writer in Chemical and Engineering News has called "collegiate capitalism." He was referring to the increasing support by industry of research conducted at academic institutions. This development has introduced a third party into the existing partnerships between many academic institutions and the

federal government. It raises many complicated questions, some of them similar to the concerns of the late forties that accompanied the entry of the federal government into support of research by academic faculties. Others of the issues, such as the possible inhibition of information exchange and potential conflicts of interest, are new.

The NIH has substantial interest in the outcome of these new relationships and there have been suggestions that the NIH become involved in some official way in them. We have not done so because we believe that these new forms of joint endeavor should continue to evolve while our role is that of a facilitator where appropriate. The areas of collaboration between industry and academic institutions have broadened and promise to grow. Industry is performing and supporting an increasing amount of biomedical research. Last year for the first time in recent years, the total funding for industrially conducted and sponsored research was greater than the NIH research budget. However, it is clearly predictable that the federal government will continue to be the principal source of funding for basic research.

In any case, the interest shown by industry in biomedical research as an investment is another evidence of growing awareness of the economic implications of biomedical research and of health care.

During the seventies, a five-year study was conducted to provide at least an approximation of the worth of biomedical research. The results were published in 1979 in a book by Selma J. Mushkin, titled

"Biomedical Research: Costs and Benefits." The study addressed the question, "Is the public getting an appropriate return for the multibillion dollar yearly expenditure on health research?"

The answer was an emphatic "yes" when the yardstick included actuarial estimates of the dollar value of the productivity of the lives saved and the years of sickness averted. For the 75-year period beginning in 1900, the ratio of total cumulative benefits to total research and development costs was about 13 to 1. In more recent years since 1930, the ratio was 5 to 1. The recent somewhat lower but substantial return reflects the costs of the large amount of basic research conducted during the past 40 years. The payoff from such research is certain to strongly and favorably affect future ratios of benefits to costs. Current expenditures for basic research are long-range investments.

In just one area, recent events have highlighted other beneficial and tangible effects of the national expenditures for biomedical research. For example, in the past seven or eight years, a totally new industry has emerged from the employment of the recombinant DNA, cell fusion, and related technologies. Incidentally, these new procedures and technologies were developed with public funds. In just one year, in 1983, a billion dollars was invested by the private sector for the commercialization of the products of these new discoveries.

In the context of these economic benefits, we encounter a paradox; namely, that a number of medicine's discoveries in recent years have increased rather than decreased the cost of medical care. This is an aspect of the economics of research about which there has been considerable public discussion of late. The argument is made that measures such as heart and liver transplants and expensive futuristic diagnostic techniques could lead to vast additional health expenditures over the next generation.

Last summer during a press conference in a discussion of the rapid increase in the cost of medical care, I speculated facetiously that someone will someday suggest to the Office of Management and Budget that the best way to control health care costs is to shut down the NIH. This was reported in the Los Angeles Times. About two weeks later, I received a letter from Harry Schwartz, long with the New York Times and now a writer and lecturer on medical issues. He reminded me that my prediction had been fulfilled before I made it--that he had been the someone who would suggest shutting down research to save on the cost of medical care. He sent me a copy of his article that appeared in the Wall Street Journal, April 3. "Do we really want medical progress," the article began, "or should we start thinking seriously of closing the National Institutes of Health and other public and private facilities now doing research to cure diseases and prolong lives?"

In his letter to me, he repeated what he calls 'Schwartz' first law of medical economics' that reads, "In health care, the ultimate economy is death."

In the face of all this, I remain an optimist and believe that if we persist, one by one these expensive halfway technologies that are now lifesaving will be rendered as obsolete as the iron lung and will be replaced by simple inexpensive and effective measures. But we must continue to search.

In this discussion of biomedical research and medical education, as well as the forces affecting them, my point of reference has mainly been the medical school. But the relationships discussed are reciprocal. Certainly the federal support of biomedical research has had its effect on academic medicine--but medical school faculty members and their supporting personnel have made possible the extensive research programs of the National Institutes of Health.

Medical practice plans have influenced the selection of medical school faculty and have bolstered the support of medical education. And, at the same time, members of the faculty practice plans have formed the core of excellence of some of our finest tertiary care health centers.

Similarly, as I mentioned earlier, medical schools have been the beneficiaries of industrial support for research, but the returns to industry from such investments have been direct as well as indirect.

And finally, in pursuing these complementary relationships, one addresses the bonds between research and education--ties so close that advanced education is essentially indistinguishable from research. Freestanding research institutions like yours and the laboratories of intramural NIH are in fact advanced centers of learning. All such institutions share responsibility for preserving the findings of the past as a dynamic resource for serving the needs of the present and for molding the future of science.

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[1]John E. Deitrick, M.D., and Robert Berson, M.D., Medical Schools in the United States at Mid-Century, McGraw Hill Book Co., New York, 1953, p. 46.

[2]Deitrick, p. 99.

NEW CHALLENGES IN OUTPATIENT RESEARCH AND TRAINING*

by

James B. Wyngaarden, M.D.**

I am delighted to be here today to join in dedicating the new outpatient unit for the Dallas General Clinical Research Center (GCRC), and to participate in the naming of the conference room, and the unveiling of the portrait of Donald Seldin.

I have enjoyed watching the evolution of Southwestern Medical School through periodic visits to Dallas and a continuing observation of its accomplishments. From humble beginnings just over 40 years ago, it has grown not only in size and in physical structure but more importantly in intellectual and academic standing until it now ranks among the top institutions of this country. Perhaps I am best qualified to speak of the Department of Internal Medicine, since that is my own discipline. Under Don Seldin's extraordinary leadership, the medical department of Southwestern has become in my view and that of many of my colleagues the number one research Department of Medicine in this country, and therefore quite possibly in the world. And the research done in this department is clearly focused. It is research using the most sophisticated and probing methods of modern science in the exploration of

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**Director, National Institutes of Health, Bethesda, Maryland.

human disease problems--clinical research of the most exacting type, measuring up to the very high standards that Don Seldin has always inspired and insisted upon. His eye for young talent and his ability to recruit and nurture that talent lie behind the success of his department, and in a parental way account for our being here to dedicate this facility today.

The research results coming out of this GCRC, of course, mean much to the investigators and other specialized staff here who are dedicated to clinical research and the improvement of patient care. And the GCRC means much to the patients and families who have been helped by diagnostic and treatment advances developed here. For example, scores of patients with recurrent kidney stones have benefited from the work of Dr. Pak and his group. And when I refer to Dr. Pak's group, I say it with full recognition of the unique contributions of his colleagues and the specialized nurses, dietitians, and technicians who are called upon to employ great skill and understanding in the conduct of research and the operation of this unit.

This GCRC and its new outpatient unit mean a great deal to all who are gathered here today, but in a larger context, the GCRC represents much more--to the Health Sciences Center of which it is an integral part and to the Federal Government, specifically the National Institutes of Health, in our partnership aimed at gaining new knowledge to improve diagnosis, treatment, and prevention of disease.

The Academic Health Center has much to gain from its research component, for the linking of research and teaching is valuable to

both enterprises. Education is diminished if it does not expose students to committed scholars and researchers. Moreover, the research enterprise gains from the presence of the teaching element, for students with fresh ideas often stimulate their mentors in the exploration of new avenues. The health care component of the academic center and the research undertaking also provide mutual enhancement.

The auditorium of the NIH Clinical Center has a quotation carved in the marble wall at its entrance, a quotation from its first Director, Dr. Jack Masur, for whom the auditorium is named, which beautifully captures this concept. It reads: "Hospitals with long traditions of excellence have demonstrated abundantly that research enhances the vitality of teaching; teaching lifts the standards of service; and service opens new avenues of investigation." That statement could as well be carved on the walls of the Dallas GCRC.

The general clinical research centers--which are fully grounded in the history and philosophy of the NIH--individually are microcosms of the NIH/medical school partnership. Each includes core support for investigators funded through NIH project grants, and a strong training element as well. They represent NIH's commitment to stability of the research environment, to investigator-initiated research, and to the future of the research enterprise through training.

The GCRC program at the NIH had its origins in 1959 when the U.S. Senate Appropriations Committee, perceiving the need to increase patient-oriented research, urged that clinical research

centers be established throughout the country to improve and intensify the scientific attack on man's diseases and their basic biological mechanisms. A $3 million appropriation created eight centers in 1960; by 1962, when the Division of Research Facilities and Resources assumed responsibility for the program, it had grown to 60 centers. By 1966, 93 centers had been established.

Subsequent to this period of growth, a number of needs and opportunities arose for improving and enhancing operations. Changes included implementation of a policy to allow for third party payment for some patients and to make the use of beds more cost effective.

Outpatient studies were introduced into the GCRCs in 1971 as a means of expanding clinical research at reasonable cost. Not only does research involving outpatients allow a greater latitude in clinical research protocols, it also allows for greater use of the GCRCs while conserving precious and expensive bed space. Studying ambulatory patients places different research and staffing requirements on the GCRCs, but by 1979 some 56 centers had made adaptations to handle the outpatient flow. Now two of the GCRCs are entirely devoted to research involving outpatients, and the number of outpatient visits in the GCRCs combined climbed dramatically from 1,175 in 1970 to about 120,000 now. The outpatient facet has contributed greatly to our knowledge of clinical medicine and has given investigators clinical information that studies of inpatients could not have yielded. Population studies, follow-up of former inpatients, and clinical trials involving

hundreds of patients, for example, are well suited to the outpatient research facilities at the GCRCs.

The outpatient research element of the GCRC program has been very productive in terms of scientific knowledge gained. It has contributed to a dramatic increase in scientific papers from GCRCs published in major journals.

The Dallas GCRC even now has an impressive listing of published scientific articles based on outpatient research conducted by investigators whose research covers a spectrum of diseases --diabetes, hypertension, lipid metabolism, kidney disease, and mental disorders. With your new capacity for 5,000 outpatient visits a year, gains in scientific knowledge should be even greater. Better still, the availability of this fine facility should attract new investigators--who have never before used the GCRC--to design studies to take advantage of the new opportunity presented.

Such changes in the approach of GCRCs over the years, as well as intensified application of the principles of peer review, have resulted in a program substantially different and improved from its counterpart of a little more than a decade earlier: In 1970 there were 983 centers with 904 beds, funded at a level of about $35 million. The number of centers dropped gradually to 75 in 1984 with 595 beds funded at a level of about $64 million.

The GCRCs support 80 percent of the patient-oriented research for the extramural program of the NIH categorical Institutes. The two largest groups of users in the GCRCs, taken as a whole, are investigators supported by grants from the National Heart, Lung,

and Blood Institute (NHLBI) and the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). This latter Institute alone supported some 700 projects that utilized the GCRC facilities, accounting for the heavy concentration of endocrine and metabolic studies at the GCRCs. This is reflected in the Dallas GCRC. Dr. Pak's studies, for example, are supported in part by the NIADDK, and cardiopulmonary studies and research on lipid disorders are funded by the NHLBI. (Dr. Pak, by the way, came to Dallas from the NHLBI intramural laboratories.)

In national terms, more than 3,500 projects are conducted at GRCR centers each year by a small army of investigators, most of whom receive support from NIH research grants, training grants, program project grants, contracts, or Career Development Awards.

It is a testimony to the importance of the research going on at the Dallas GCRC that it has a broad base of support that goes beyond the NIH and other Federal agencies--many projects are funded by the private sector, including industry, associations, and foundations.

The future of clinical investigation depends upon an adequate supply of well-trained investigators dedicated to clinical research. Recognizing this, the GCRC program in 1974 initiated the Clinical Associate Physician (CAP) program. This program, designed to encourage young physicians to enter careers in clinical investigation, has since produced 97 graduates, of whom approximately 80 percent have remained in academic medicine. To date, one-half of theses graduates in academic medicine have obtained NIH support for their clinical research investigations.

In addition, the GCRC program has for the past five years had a very popular medical student program which provides exposure to clinical research for periods of three to six months.

The GCRCs constitute a unique environment for a very special kind of research--indeed a very special kind of clinical research. Because of its very nature, the GCRC provides an atmosphere where the many paths of inquiry and discovery about life processes, particularly those which stem from efforts to understand and intervene in states of disease, can flourish. Almost everyone can appreciate the contributions to human health gained through the "bench to bedside connection." But that is only one possible path to scientific discovery. The GCRC provides a milieu in which the path of inquiry can flow in the opposite direction--from "bedside to bench," producing major advances in our understanding of fundamental biological phenomena. A fine example is the study here demonstrating that thickening of the capillary basement membrane is reduced after long-term control of glucose levels. This study not only has implications for reducing the many complications of diabetes, it also has contributed to our fundamental knowledge of this ubiquitous structure.

Many have expressed their concerns in recent years about the future of this two-way flow--"bedside to bench" and "bench to bedside." Dr. David A. Hamburg, former President of the Institute of Medicine, put it well in 1980: "We must do everything in our power to see that the great fundamental advances--indeed the inspiring advances in molecular and cellular biology--will be available as soon as possible for health interventions of a

demonstrably useful character. But the authentic biological revolution that has been generated by several decades of intensive basic research is not easily translated into clinically valid applications. An interpreter is needed, and it is the clinical investigator who serves that function. The flow of information is by no means unidirectional; if basic science has something to say to clinical investigation, so too does clinical investigation offer much to basic science. Clinical research remains the vital bridge between advances in basic science on the one hand and improvements in health care--diagnostic, therapeutic, or preventive--on the other."[1]

For its part, the NIH has an array of training and career development programs that are especially attractive for M.D.s. Our 20-year-old program for combined M.D./Ph.D. students, known as the MSTP or Medical Scientist Training Program, has been very successful in terms of building up clinical research. An informal survey of 66 graduates of the program from three schools showed that one-third had gone into basic research departments and two-thirds were in clinical departments. Of those in clinical departments, one-half were engaged in clinical research with human subjects.

The NIH also has other programs that provide early exposure to research careers. This past year over 1,100 medical students

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[1]Conference Summary, "Clinical Investigation in the 1980's: Needs and Opportunities," Institute of Medicine, National Academy Press, June 1981, p. 2.

availed themselves of off-quarter training opportunities supported by NIH. With the new exemption of the first year of NRSA support from payback obligation, the NIH has reinstituted the post-sophomore fellowship or its equivalent, and thus provides a full year of research training within the medical school experience under an NIH fellowship or traineeship. The NIH also offers Summer Research Fellowships at Bethesda, and during this past year over 50 medical students participated in that program.

A new addition to the Career Development Award series is the "Physician-Scientist Award," designed to provide five years of phased supervised research development. Made primarily as an individual award, these programs will be based in departments with established records in producing physician/scientists. The first two to three years must be under the guidance of a sponsor who is a basic scientist. The second phase, undertaken at a more independent level, is intended to provide support during transitional years when the awardee will establish a personal research program. The program is sponsored by eight NIH Institutes. This program does not replace current training or fellowship programs and is smaller in scale, perhaps leveling off at approximately 2,900 awardees in three years. It complements the MSTP program in providing graduate school level experience for the professional degree holder who begins at a post-medical school stage.

We at NIH are especially enthusiastic about our newest program to provide for the future of clinical research--a joint project with the Howard Hughes Medical Institute (HHMI) to support research training for up to 30 medical students a year on the NIH

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campus, working with leading NIH intramural scientists for periods of six months to a year. Although these two programs are just beginning, it is expected that they will help ensure a supply of physician investigators for the future.

It is most gratifying to note that a third member of the medical science partnership--the private sector--is beginning to participate in programs and support for clinical investigators of the future. I am especially happy to learn that this GCRC is undertaking its own innovative program to train young investigators in clinical research through the General Clinical Research Support program--entirely supported by generous donors from the private sector. The program is unique in that it will offer medical students, medical residents, and M.D./Ph.D. candidates exposure to clinical investigation. It is likely that a significant number of them will be stimulated to undertake careers in clinical investigation, and others, no doubt, will come away from their research rotation with a better understanding of clinical research.

In closing, I want to commend the GCRC and the University of Texas Southwestern Medical School for all that has been accomplished here through inspired leadership and a dedicated and outstanding faculty and staff. I congratulate all of you who played a role in achieving the goals you have set for your program with the establishment of the outpatient unit.

Thank you for the opportunity to attend and participate in this dedication.

REMARKS

by

JAMES B. WYNGAARDEN, M.D.

It was during my freshman year as NIH Director that I had most frequent contact with John. He was serving then as Acting Director of the Dental Institute. In a short time, I learned to value highly his broad knowledge of the Institute--its opportunities and the issues surrounding it. More than that, I gained a special appreciation for his quiet integrity and sound judgment--qualities well known to his longtime associates--and quickly recognized by the Bureau, Institute and Division Directors when he began meeting and working with them on a regular basis when he served as an Acting Director.

At the time Dr. Löe was sworn-in as the fifth Director of NIDR in January of 1983, I called attention to the dynamic leadership that John had provided for over a year as Acting Director. I feel sure that Harald better than the rest of us can appreciate the sure-handedness with which John had conducted the Office of Director in the interim. But to dwell exclusively on his outstanding record as an administrator, having served in several of the major NIDR posts, is to fail to do justice to John's research on the chemistry of connective tissues where he has made substantial contributions to knowledge of this important subject.

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*Presented upon the retirement of Dr. John D. Goggins as Deputy Director of the National Institute of Dental Research, September 27, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

Because John's departure represents a substantial loss to the NIH, I felt that, as a responsible executive, I could do no less than conduct an unofficial investigation of the circumstances. I assigned this responsibility to a member of my staff who has reported three findings to me: First, I was told that the tip-off to members of the NIDR staff that John was leaving came when he sold his venerable Volkswagen bus. That vehicle was considered by all concerned to be indispensable for its time-honored service in hauling the beer to the annual NIDR picnic. The second finding reported to me was that the real reason that John has made this major career change--and will move to a seaport on Lake Michigan--is to justify to his wife, Madeleine, the purchase of a new sailboat.

Finally, and this is more in the nature of the results of an opinion poll than the findings of an investigation -- in my operative's words, "It was the unanimous opinion of a significant sample of NIHers that 'John Goggins is too nice a guy to become a dean.'"

Our feelings about deans notwithstanding, John -- we congratulate you and we are delighted to see you receive this deserved professional advancement and recognition.

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REMARKS*

by

James B. Wyngaarden, M.D.**

During most of my professional career and indeed for a large portion of my life, I have been closely associated with a teaching hospital and engaged in research. Consequently, I feel perfectly at home in a meeting of hospital personnel and can understand the sense of common purpose that sets you apart from other organizations. While you are members of the NIH community, you have, in addition, a special identity as members of the Clinical Center family. What you do has added meaning; for whatever your occupation here may be, it plays a real part in providing the finest of medical care to our patients. Furthermore, from the research conducted here can come significant benefits for people everywhere.

In a short time--in weeks, I am told--a new book about intramural NIH will appear. The foreword was written by the distinguished physician, scientist, and author, Lewis Thomas. Because the Clinical Center plays such a central role, Dr. Thomas's praise for the intramural program applies especially to you and your colleagues.

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*Presented at the Clinical Center Awards Ceremony, Masur Auditorium, October 4, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

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After pointing out that the NIH is not only the largest institution for biomedical science on earth and that he considers it to be one of the nation's great treasures, Dr. Thomas observed that the NIH is "a standing proof that, at least once in a while, Government possesses the capacity to do something unique, imaginative, useful, and altogether right."

Regarding the intramural program particularly, he said that ". . . for sheer excellence and abundant productivity, the institution cannot be matched by any other scientific enterprise anywhere."

The Clinical Center deserves a full share of that praise.

To be selected on the basis of merit for special recognition in any organization of this quality is honor indeed. I salute and congratulate each of today's awardees.

REMARKS*

by

James B. Wyngaarden, M.D.**

Dr. Lindberg, Mrs. Lindberg, Jonathon, other members of the Lindberg family, colleagues, and distinguished guests:

I can well imagine that Don may have been of two minds when considering our offer of the directorship of the National Library of Medicine.

On the one hand are the attractive features. Not necessarily in priority order, there are the facilities--two beautifully and practically designed buildings, including this splendid auditorium. There is the Library's nearly 150-year history--giving its modern accomplishments the deep, rich soil from which to spring, and the perspective from which to guide the high-tech promises of the future. There is the prestige of leading an organization of international renown. There is the glamour of life in cosmopolitan Washington. Perhaps I should suggest one more that Don is probably only now beginning to appreciate, and that is the superb and dedicated staff of the Library. At this point, I must add a note of personal thanks here to Dr. Harold Schoolman and Mr. Kent Smith for their superb performance during the interim directorship and the many months of the selection process.

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*Swearing-in Ceremony of Dr. Donald A. B. Lindberg, Director, National Library of Medicine, Lister Hill Center Auditorium, October 5, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

On the minus side, perhaps, of an assessment of the post of Director, NLM, is Government bureaucracy--sometimes more cumbersome even than that of academia. Terms like "freezes" and "A-76" will become prominent in the Director's vocabulary. Also, there is the shadow of Marty Cummings' achievements after a 20-year directorship--pretty big shoes to fill. And most of all, there is the awesome responsibility for not only acquiring all of the world's medical literature but of getting it out to everyone who needs it--students, practitioners, and researchers.

If Don did hesitate, I'm sure it was just for a moment, because those areas that seem like minuses to some would be seen as beckoning challenges to a man like Don. The reason this is true, I think, is that he knows himself and he knows the job--from the many years of working with the Library and NIH as a consultant and friend.

Don Lindberg's qualifications as a teacher, administrator, pathologist, and computer expert are spelled out in the program. To recapitulate briefly--a graduate of Amherst College, he received his medical degree from the College of Physicians and Surgeons of Columbia University. He has been associated with the University of Missouri for over 20 years--as a teacher of pathology and of library and information science, and most recently as Director of the School of Medicine's Information Science Group.

(Here, Dr. Wyngaarden quoted Dr. William D. Bradshaw, Dean, University of Missouri Medical School: "We are extremely pleased that one of our best has been chosen for this very noteworthy position. We are very proud of him and wish him every success and that all his problems be small.")

What isn't reflected in the program is his humanism--a humanism that recognizes that technology is a tool to serve people, and that like medicine, there is art as well as science involved in information technology. The magic of the electronic age is not really magic, of course, and the work and expense of this high-tech vision must be rigorously weighed against the concrete benefits that are promised. Don has often made this distinction between the computer age vision, which he knows so thoroughly, and the necessity to count the costs. As a dreamer, he can see the future; but as a decision maker, practical, service-oriented considerations will rule his judgment.

As many of you know, one thing the Library is famous for is its penchant for acronyms--MEDLARS, MEDLINE, MeSH, and dozens more. Don was somewhat concerned about his initials--"DABL"--but I assured him we knew he would take his job most seriously.

The Library's first Director was Dr. John Shaw Billings, who served for 30 years from 1865 to 1895. As I noted earlier, Dr. Cummings served for 20 years. Dr. Lindberg, here, is a young man, and I don't think it's too much for us to expect that he will take the Library into the second millennium--that's only 15 short years away--and beyond.

Whatever his length of service to the Library and its worldwide constituency, I know that he will make a significant and positive impact on its history. And I welcome him and his family into the NIH community.

REMARKS*

by

James B. Wyngaarden, M.D.**

Most persons--whatever their organizational experience--would be surprised at the volume and variety of work carried out by the several components of the Office of the Director, NIH. Certainly I was. A second, more pleasant discovery for me was the capability of the staffs within the OD as demonstrated through the quality and quantity of the work they perform.

As Director, I have the pleasure of participating in various award ceremonies. It is always fascinating at NIH to note the range of occupations represented by the persons receiving awards. And even in the Office of the Director, which has no laboratories or clinics, recognition is being given to a surprising variety of occupations and accomplishments this year. To get a real appreciation of this, I suggest that as you listen to the reading of the citations, you visualize the activities of the awardee for which the honor is given.

In addition to specific accomplishments, I have come to value highly the rich resources of experience and good judgment residing in the people of the Director's Office. One superb asset we seldom discuss is the skill that is quietly demonstrated from time

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*NIH-OD Merit Award Ceremony, Wilson Hall, October 9, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

to time in coping with or perhaps short-circuiting overly bureaucratic procedures. In this connection, I have learned that there are some questions a Director should not ask.

All of us in this office have a common responsibility, that basically is to provide administrative support in its broadest sense for the real work of NIH--the research that takes place in the laboratoreis and clinics, intramurally and extramurally. This support takes many forms, and although its product may not be the subject of a journal article or its significance recognized by medals or scientific prizes, it is absolutely essential.

I am acutely conscious that there are fewer awards being made today than the number of persons deserving them. I hope that each of you will view this ceremony as honoring everyone assigned to the Office of the Director. At the same time, I extend my heartiest congratulations and special thanks to each of the honorees.

BASIC RESEARCH AS AN INVESTMENT IN COST-EFFECTIVE HEALTH IMPROVEMENT*

by

James B. Wyngaarden, M.D.**

It would be difficult to improve on the cost-effectiveness of the health care system described by Herodotus some 2,450 years ago. In writing about the Babylonians, he told of what he considered to be one of the wisest of their customs. "They have no physicians," he said, "but when a man is ill, they lay him in a public square and the passersby come up to him. And if they have ever had this disease themselves or have known anyone who has suffered from it, they give him advice, recommending him to do whatever they found good in their own case or in a case known to them. No one is allowed to pass the sick man in silence without asking him what his ailment is."[1]

Undeniably, this form of treatment was inexpensive. Furthermore, it represented probably the most enlightened therapy of the day. The sad fact is that as recently as the early 1900s, medical practices in this country were little better than the Babylonian method and in some instances they were worse. For it was at the beginning of this century when thoughtful clinicians began to recognize that almost all of the complicated treatments

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*Presented at the Institute of Medicine Annual Meeting, Washington, D.C., October 10, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

long in common use did not work, and that many of them actually did more harm than good.

In the wake of the virtual revolution in the practice of medicine that has happened in the past fifty years, however, we have seen the development of a new array of complicated diagnostic procedures and treatments.

We are experiencing a kind of repeat of the medical history of the nineteenth century, but with a major difference. The many complicated, expensive, and often painful treatments of that day were of little if any benefit. Some procedures today may be complicated and expensive, but they are also powerfully effective.

The satisfaction we are justified in feeling about the many innovations of medicine is intruded upon, however, by our uneasiness over the economic as well as other stresses they may generate.

As the technology and complexity of medicine have increased, medical care has become more highly specialized and institutionalized. There is a widely held view, particularly among nonphysicians, that the increasingly sophisticated science and technology of medicine have been accompanied by a decline of compassion in medicine. There is an implied conclusion that there is something inherently contradictory between science and humanity, between technology and compassion.

But in an essay published in 1981, entitled "Humanistic Medicine in a Modern Age," Glick suggests that computer tomography and diagnostic ultrasound, for example, can be viewed as technologic advances of extraordinary compassion. Their use has spared

patients many difficult, painful, and dangerous procedures and has permitted definitive diagnoses to be made earlier. One example will suffice: The exploratory abdominal laparotomy, once a regular entry on the operating room schedule, has all but disappeared as a preoperative listing.

The basic knowledge needed for the science of medicine began to be sought and found in the late nineteenth century, primarily in Western Europe. Incidentally, the predecessor to the National Institutes of Health had its beginnings in this same period. Though quite small, the Laboratory of Hygiene, established in 1887, was a part of the movement to study in detail the newly discerned roles played in disease by bacteria and viruses. The first Director of the Laboratory, Dr. Joseph J. Kinyoun, had learned the uses of tuberculin under Dr. Robert Koch in Berlin and, at the Pasteur Institute in Paris, had studied the newly developed means for preventing rabies.

Later, in writing about the emergence of antibiotics and their influence on medical practice, Lewis Thomas observed, ". . . It needs emphasizing that it took about 50 years of concentrated effort in basic research to reach this level," and "If this research had not been done, we could not have guessed that streptococci and pneumococci exist and the search for antibotics would have made no sense at all."[2]

Then focusing on the effect of such advances, the distinguished British physician and scientist, Sir Harold Himsworth, commented in 1973 that "When historians look back at the period in which we are now living, they are likely to see it

as that time in which scientific knowledge emerged from its adolescence to become a major factor in the affairs of human societies."[3]

Certainly medical science has become a major factor in human society. Even in its adolescent stage in the latter nineteenth century, there was sufficient knowledge to bring about the sanitary reforms and the development of vaccines that had such a marked effect on public health.

Indeed something profound has happened in the relatively short span of time since the early 1900s when the life expectancy for the total U.S. population at birth was 47.3 years. By 1950, marked changes had been achieved in all groups, adding 21 years. Progress has continued so that the latest tabulation--that for 1982--shows life expectancy at birth for the total population at 74.5 years.[4] The decline in mortality, particularly in the first half of this century, can be attributed more to prevention of disease than to the development of specific therapies. Much of this truly spectacular progress is due to the reduction in death rates of infants and children.

The modern era of medicine is, however, increasingly marked by successful intervention as well as prevention, and intervention is increasingly science-based. Remarkable changes took place in just one generation through the use of penicillin, the sulfonamides, and other new therapeutic measures. For example, between World War I and World War II, the death rate for all diseases in the Army, including overseas forces, was reduced from 14.4 to 0.6 per thousand. Dysentery, formerly the scourge of armies, became a

minor problem. Tetanus, typhoid, paratyphoid, cholera, and smallpox were practically eliminated. As the result of a potent vaccine and mosquite control, yellow fever did not appear in the Army or Navy in World War II. The use of sulfa drugs lowered the death rate from lobar pneumonia in the Army from 24 percent in the first world war to less than one percent in the second. The death rate from meningitis was reduced to a tenth of that in World War I.[5]

But preventive medicine today, with the infectious diseases such as smallpox, diphtheria, and polio no longer a threat to public health, faces a different and more difficult challenge: to eliminate those diseases that are chronic in nature, such as cardiovascular disease, cancer, diabetes, and kidney disease--diseases for which there appear to be no simple causes or solutions. Accordingly, prevention research has become both more comprehensive and complex. With progressive fine-tuning, epidemiologic research has opened new opportunities as risk-factors are identified that allow new and effective strategies for prevention, with concomitant reductions in health-care costs. The role of smoking in cancer, chronic bronchitis, and heart disease is a well-known example. Control of hypertension and attention to body weight, diet, and exercise play important roles in the recent reductions of mortality from cardiovascular and cerebrovascular disease. New insights into possible dietary factors in cancer give promise of possible reductions of certain kinds of neoplasms.

From its earliest beginnings, a primary goal of the NIH has been to support and conduct research that ultimately could lead to

the prevention of disease. When such efforts are fully successful, the savings in human and economic terms are great indeed. For example, the prevention of type B hepatitis through a low-cost effective vaccine could save the United States about $750 million a year, and this figure does not take into account the hepatitis B-related liver cancer that presumably would also be prevented through vaccination.

The National Institute of Allergy and Infectious Diseases has initiated a program for the accelerated development of new vaccines to bring a few high-priority candidate vaccines into use several years earlier than might otherwise be possible. In fact, the NIAID has contracted with the Institute of Medicine for advice and assistance in looking into the many facets of vaccine development and use, including cost savings. Studies are in progress on more than 50 vaccine antigens for over 30 different bacterial, viral, and parasitic diseases. Target diseases for the new program now include meningitis, gonorrhea, croup/pneumonia in infants and children, whooping cough, influenza, diarrhea, hepatitis, chickenpox, genital herpes, and malaria. Promising viral vaccines that are ready for field testing include a live attenuated influenza virus vaccine; a new vaccine for hepatitis A; a third generation hepatitis B vaccine, which should be much cheaper than the current vaccine; and a varicella vaccine.

Advances in the treatment of cancer have been remarkable. Based on scientific knowledge accumulated over several decades, therapy for cancer has improved to the point where we may have passed the 50 percent curable mark. Some of the cancers with the

most encouraging five-year relative survival rates are thyroid, 92 percent; endometrium, 87 percent; testis, 82 percent; melanoma, 79 percent; female breast cancer, 73 percent; and Hodgkin's disease, 70 percent. Much of this increased survival is due to improved therapy through chemotherapy, surgery, and radiation, sometimes in combination.

Preventive medicine has scored some remarkable triumphs but, for many diseases, gains in scientific knowledge so far have brought us only to the point of amelioration of symptoms or a slowing or halting of the progression of the process.

I do not underrate the exceptional accomplishments that many recent procedures represent. There is no way to put a price on the value of, for example, the new diagnostic procedures--including new means of chemical analysis in the laboratories, new applications of X-rays, the CT scan, PET scan, ultrasound, and soon NMR, or of coronary bypass surgery, dialysis, kidney transplants, joint replacement, advanced intensive care, and the postponement of death from liver failure, brain injury, etc. These and many other highly technical procedures for diagnosis and treatment now coming into frequent use are truly miracles of modern medicine, but often they are very expensive and constitute a powerful force driving upward the cost of medical care.

But in the context of these developments, we encounter a paradox; namely, that a substantial number of medicine's discoveries in recent years have <u>increased</u> rather than <u>decreased</u> the cost of medical care. Experts in health care and research are warning that costly medical procedures--coronary bypass surgery,

sophisticated new imaging systems, heart and liver transplants--could result in vast additional health outlays in the next decade. The challenge before us is to find means for going beyond the highly expensive halfway point in treatment.

Perhaps the best and certainly the most frequently cited example of the benefits of finding the complete solution to a medical problem is symbolized by the polio vaccine which made the iron lung obsolete and virtually eradicated paralytic polio.

The prospect of such a salutary course is not yet so bright, however, for end-state renal disease, our current prototypical example of a stalled half-way technology. Nowhere is the economic effect of our imperfect medical knowledge more clearly illustrated than in this example. Dialysis is very expensive, it does not cure the disease, reverse it, or return patients to a normal state of health. It is an imperfect solution based on an intermediate level of understanding made necessary because of our lack of fundamental knowledge about the origins and processes of kidney failure, and how to intervene successfully. If we were able to prevent kidney failure, we would save, in this country alone, approximately $2 billion annually for maintenance dialysis therapy. Other instances where imperfect, costly half-way technologies continue to drain the health care dollar include coronary bypass surgery, cancer therapy, and joint replacement.

All of the procedures I have just mentioned are effective to a point, but very expensive. The ultimate answer to the disease problems they address must be either preventive or truly curative medicine.

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Advances stemming from fundamental research offer high promise for the future. A few examples will suffice. Recombinant DNA technology has opened doors at practically every level of medical research. Monoclonal antibodies produced by hybridomas facilitate the development of vaccines, improve diagnostic tests, enhance the immunotherapy of infectious diseases, and provide powerful tools for the diagnosis of and treatment of cancer. The discovery of oncogenes and the recognition that they are found normally in the cells of all animals including humans may presage understanding of the molecular mechanisms by which oncogenes act to transform cells, and the ways they regulate gene expression. Such knowledge should open new avenues of therapy. The tremendous growth in our knowledge about neurotransmitters and neuroreceptors in recent years is providing insight into the mechanisms underlying the normal learning process, various psychiatric disorders, and the dementias. Our growing understanding of slow virus diseases underlies tantalizing hypotheses about the causes of such diseases as multiple sclerosis and Alzheimer's disease. The isolations of human RNA tumor viruses--HTLV-I and HTLV-II--from patients with certain types of leukemia/lymphoma, and of another retrovirus, HTLV-III, from patients with AIDS, offer new challenges to the development of antiviral agents.

But in spite of such examples of exhilarating discovery, the list of human diseases for which there are as yet no definitive measures for preventiion or cure is still formidable. Fresh insights into the nature of these diseases are needed. And these insights can come only from continued basic research. I do not

believe that there is an abundance of scientific knowledge locked in the laboratory merely awaiting a new emphasis on human application as some have claimed. Most of the critical bits of knowledge have yet to be discovered.

Ultimate success in curative or preventive strategies depends on the continued striving of thousands of scientists. There could hardly be a more sound investment for society than the support of such research.

At this time, the Federal Government conducts or supports 52 percent of health-related research and development in this country. Industry is responsible for 39 percent, with foundations and voluntary health agencies funding less than 10 percent.

The dominant role of the Government is at the same time complementary to and partly determined by the interests of the other participants. Industry, for good reason, gives high priority to developmental and product-related research.

In the past decade there has been a marked increased in industrial support for research conducted in academic institutions. Thus, a third partner has joined the long-standing Federal/academic cooperative research relationship.

Nevertheless, the Federal Government will continue to be the principal source of funding for basic research, because the long-term economic strength of the nation and the continued improvement in the well-being of its citizens require a sustained investment in basic scientific research, and there is no other adequate source.

Recently, I participated with Bill Schwartz in a program at the International Congress of Nephrology where there was much discussion of the economics of technology and the cost of medical care. During a press conference that Bill and I held after our presentations, I speculated facetiously that someone will someday suggest to the Office of Management and Budget that the best way to control cost is to shut down the NIH. This was reported in The Los Angeles Times. About two weeks later, I received a letter from another Schwartz, this time Harry Schwartz, long with The New York Times and now a writer and lecturer on medical issues. He pointed out that my prediction had been fulfilled before I made it, that he had been the someone who would someday suggest shutting down research to save on the cost of medical care. He sent me a copy of an article of his that appeared in The Wall Street Journal, April 3. "Do we really want medical progress," the article began, "or should we start thinking seriously of closing the National Institutes of Health and other public and private facilities now doing research to cure diseases and prolong lives?"

In spite of the high cost of contemporary medicine, I remain optimistic not only about the future of NIH, but also the future of medical care, and believe that if we persist, one by one these expensive technologies that are now lifesaving will be rendered as obsolete as the iron lung and replaced by yet more effective, simpler, inexpensive measures. But we must continue to search.

In closing, permit me to use the familiar quotation from Lewis Thomas, in which he added "halfway technology" to our lexicon and stated a truth about which we need to be reminded

periodically. Here are his words: "I say that we must continue doing biomedical research on about the same scale and scope as in the past 20 years with expansion and growth of the enterprise being dependent on where new leads seem to be taking us. It is an expensive undertaking . . . but it is still nothing like as expensive as trying to live with the halfway technologies we are obliged to depend on in medicine today; if we are to try to stay with these for the rest of the century, the cost will go through the ionosphere."[7]

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REMARKS*

by

James B. Wyngaarden, M.D.**

Marty, according to my sources, Herbert Abrams has succeeded; and the portrait we are about to unveil is a good likeness--a true expression of your dynamic personality.

The story is told that some years ago at Yale when the impressive new Sterling Library Building had just been completed, it became customary for townspeople to stop in the street and stand about admiring and commenting on the structure. For some reason, the librarian was offended by this habit, and one day he decided he'd had enough. He charged to the steps in front of the building and startled the passersby with the irritated shout: "What you see is not the Sterling Library--the Sterling Library is within!"

As counterpoint to the Yale story, I propose the idea that the NLM building and the Lister Hill Center are graphic expressions, and are also a most expressive form of portraiture, of the man whose contributions to the NIH and to biomedical communications are so substantial and lasting.

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*Portrait Unveiling, Martin M. Cummings, M.D., Lister Hill National Center for Biomedical Communications, October 18, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

But it will be a pleasure indeed to see this more personal memento of one we so admire, respect, and appreciate--and so I am delighted that we have the portrait that shortly is to be unveiled.

COMMENTS ON THE SCIENTIFIC POLICY IN THE U.S.*

by

James B. Wyngaarden, M.D.**

The U.S. biomedical research enterprise is a diverse activity, characterized by a high degree of independence for the individual scientist, and a mixed base of financial support. A range of research laboratories is involved, in public and private universities and teaching hospitals, in private institutes and foundations, among major private businesses, and in the intramural program of the National Institutes of Health (NIH).

The Federal Government is the chief patron of biomedical research in the United States. Most of this support is channeled through the NIH. Other important government agencies for supporting biomedical research are the National Science Foundation, the Veterans' Administration, and the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), but NIH is by far the largest. In FY 1984, more than 60 percent of the health R&D performed in American universities and medical schools, and 90 percent of basic biomedical research performed in the U.S. was conducted or supported by NIH. Eighty-one percent of the NIH budget is spent in its extramural program, which supports over 50,000 scientists

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*Presented at the Symposium, "Recherche Medicale, Sante, Societe," celebrating the 20th Anniversary of the Institut National de la Sante et de la Recherche Medicale, Paris, France, October 26-29, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

in 1,250 different institutions through 22,000 grants and approximately 1,100 contracts per year.

The NIH is one of five agencies of the U.S. Public Health Service which is a part of the Department of Health and Human Services. The other agencies are the Food and Drug Administration, the Centers for Disease Control (in Atlanta, Georgia), ADAMHA, and the Health Resources and Services Administration.

The mission of the NIH is to conduct and support research of benefit to the health of the American people. The NIH is not a regulatory agency, beyond setting certain conditions for the conduct of research involving animal or human subjects, or recombinant DNA technology. It also has no direct responsibility for the delivery of health care, except as that is a component of research, for example, in clinical trials.

The system for support of scientists is indirect in that the Federal Government does not finance the careers of scientists per se. Rather, support from the Federal Government depends upon their competing successfully for NIH research project grants, which are made to their institutions. These project grants usually include salary support for the scientists and staff involved, depending upon the level of effort during the conduct of the research project.

While this system has operated successfully for many years, it can create instability for individual scientists, since the average grant has a life of three to four years, and investigators must compete for renewed support.

Recognizing the importance of assuring scientists at various career decision points that support funds are available and that research careers are feasible, NIH has for several years operated under a "stabilization policy" whereby we have endeavored to dampen large fluctuations in support of new and competing research awards. The key factor in the system, of course, is the amount of the annual appropriation to the NIH; and to put this policy into action, it has been necessary at times to curtail other types of funding mechanisms.

After a period of spectacular growth from 1943 through 1965, when the NIH budget grew at an average rate of 24 percent per year in constant dollars, the budget has leveled off at an average real growth rate of about 2 percent per year from 1965 through 1984. In giving first priority to investigator-initiated research projects, NIH has shifted funds to the research project grant category annually since 1974. This category has grown from 62 to 83 percent of the extramural budget in about a decade; contract and training categories have been correspondingly reduced.

The U.S. system for setting biomedical research priorities is pluralistic, involving many forces. The areas of emphasis for biomedical research are shaped by a number of factors. Our emphasis on investigator-initiated projects encourages diversity and excellence in health research; it relies upon the scientific community itself to identify, through a competitive peer review process and review by non-government scientists, the ideas and investigators most worthy of support. In this way, public funds invested in biomedical research support the most creative ideas

and energies in the American health research community--a wealth of ideas whose range far exceeds those that could be generated by any single committee, board, council, or laboratory.

In setting research priorities, we also give major consideration to the concerns and wishes of the public, expressed directly and through Congressional and Executive Branch actions. Authorizing legislation, mandates, directives, and appropriations language all influence our research planning and the conduct of our programs.

Another important part of the planning process takes into account the views of professional societies and voluntary health organizations, the biomedical research community, and the general public. These views are sought through structured activities such as national advisory councils, task forces, or commissions to consider specific research areas or health programs. NIH staff also plays a key role in setting priorities, through five-year planning exercises, and by soliciting specific research proposals from the scientific community when there are gaps in knowledge not being spontaneously addressed through investigator-initiated projects.

Because of its role as the principal arm of the Federal Government for biomedical research, the NIH must be concerned with the future of biomedical research in the U.S. For that reason, we support an array of training and career development programs that can carry aspiring scientists from a short-term research experience in graduate or medical school through several levels of more independent research training, thus enhancing their ability to conduct the increasingly complex and advanced research now taking

place at the frontiers of knowledge. Each year NIH supports 9,000 to 10,000 young scientists in training, and another 1,300 to 1,400 persons in more advanced development programs.

The NIH has supported research internationally as well as within the United States; science is universal and the applications of discovery are useful to all people. We readily defend the support of outstanding science wherever it is performed as being of potential benefit to the American people, just as we hope discoveries in the U.S. are of benefit to people everywhere. Following the receipt of the Nobel Prize by the Pasteur Institute group, Jacques Monod publicly stressed the considerable role that U.S. financial support had played in making their work possible. For the past 15 years the amount of the NIH budget devoted to international programs has remained steady at about 1.5 percent of the total. About one-half of this, approximately $30 million in FY 1983, was in the form of grants-in-aid to foreign scientists, and about one-half in support of training of foreign scientists in the U.S., and related travel, conference, and administrative expenses. For example, in FY 83 there were 80 French nationals in our visiting fellowship and guest worker programs at the NIH.

REMARKS*

by

James B. Wyngaarden, M.D.**

On behalf of the National Institutes of Health, I wish to offer condolences to our Indian colleagues on the death of Prime Minister Indira Gandhi.

Mrs. Gandhi, long admired as a distinguished leader of a great country, showed vision and sensitivity. She appreciated the role that science and technology played in improving the life of her people. During a visit from a U.S. delegation in late Octoberr 1982, of which I was a member, Mrs. Gandhi demonstrated her knowledge of science and its key role in helping India solve some of its critical health, food, and energy problems. She also emphasized her concern for leprosy, which affected 3.5 percent of Indians; problems with nutritional blindness and early cataracts in India; and her country's ability to produce enough food for its expanding population.

I had the pleasure of meeting with Mrs. Gandhi on three occasions--twice in Washington, D.C., and again with the delegation to Delhi two years ago today. She was a friend of the United States, and the leader of the nonaligned. Her death brings great sadness to her friends worldwide.

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*Memorial tribute to Prime Minister Indira Gandhi, ACRF Amphitheater, October 31, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

Introductory Remarks for NIH Lecture

It is my pleasure tonight to welcome to the NIH Dr. Fernando Nottebohm, this evening's speaker in the NIH Lecture Series.

Dr. Nottebohm is director of the Rockefeller University Field Research Center for Ethology and Ecology. He has been at Rockefeller since 1967, soon after he received his doctorate in zoology from the University of California at Berkeley. He is a fellow of the American Association for the Advancement of Science and of the American Academy of Arts and Sciences.

Dr. Nottebohm's lecture "Neuronal Replacement in Adulthood: Its Possible Relation to Learning," raises the exciting possibility that the brain may generate new cells throughout life. This challenges the currently held beliefs that by the end of infancy, the brain has all of the cells it will ever have, and that as brain cells die with age or are destroyed by injury or disease, they are never replaced.

To date, Dr. Nottebohn's research has focused on canaries and their songs -- a model that has permitted important and provocative observations on the brain's ability to generate cells in response to hormonal stimulation. His research has also raised some intriguing questions about sexual dimorphism in brain anatomy and function.

Dr. Nottebohn, we are looking forward to what promises to be a fascinating talk.

Masur Auditorium, November 7, 1984

THE CHALLENGES OF MEDICAL RESEARCH*

by

JAMES B. WYNGAARDEN, M.D.**

It is indeed a pleasure to make this visit to the Vanderbilt campus and to take part in the annual induction ceremonies of your chapter of Alpha Omega Alpha. I am particularly honored to have been invited to present the 1984 James Ed Holloran Address in memory of his achievement of the highest ideals of AOA while a student here, and in recognition of the bright but unfulfilled further promise of his life.

In Martin Kneece's letter of invitation, he suggested that any topic I might wish to discuss would be acceptable, but he hoped that I would share my thoughts on the challenges and problems of academic medicine and medical research today. Especially, he asked for comment on the reasons why medical students and house staff looking toward the future should or should not consider this career option. I was comfortable with his suggestion, for it is exactly the subject that I would like to discuss with you. It is in institutions such as Vanderbilt that academic medicine and medical research fully play out their mutually reinforcing functions. Here we have a demonstration of how the alliance between the Federal government and academia through the NIH has been such a powerful force in the advancement of science in this country.

For the first 50 years of its history, the National Institutes of Health had little direct contact with academic institutions. Essentially it was a freestanding, independent laboratory of limited size. Only after World War II did the Agency begin growing at the spectacular rate that saw the prewar appropriation of less than half a million dollars increase by a factor of more than 10^4 to reach our current annual appropriation of more than five billion dollars.

This growth would not have been possible in the absence of the partnership between government and academic institutions for the conduct of biomedical research. The partnership was initiated out of necessity. In responding to the sudden wartime needs for research of the health problems of the armed forces, the military turned to the established academic laboratories for the conduct of vital studies. By grants and contracts, academic scientists were in effect mobilized for the support of the war effort. The arrangement worked. It worked

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*1984 James Ed Holloran Alpha Omega Alpha Address, Vanderbilt Medical School, Nashville, Tennessee, November 8, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

extremely well. The new partnership greatly accelerated biomedical research and development from the most basic studies to the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

In 1945, with demobilization, the ongoing contracts and grants for biomedical research underway at academic and other nonfederal laboratories were transferred to the NIH for administration. These projects formed the nucleus of a new dimension for NIH activities; that is, the sponsorship of research conducted in academic institutions by nonfederal scientists. These extramural activities quickly became the primary mode of operation of the rapidly growing Agency. In recent years, 80 percent of our total budget has been used for the support of extramural activities through research grants, training grants, and contract awards. For the past decade, about three-fourths of all NIH awards have been made to universities, medical schools, and other academic institutions and a little over one-half of all such awards have been made for members of medical school faculties. In 1983, the last year for which we have complete information, Vanderbilt University and School of Medicine received almost 30 million dollars in research grants, contracts, and training awards.

Concurrent with the development of this government/medical school partnership, and certainly in large measure as a result of it, there has been amassed an incredible store of biological knowledge, not to mention tremendous advances directly relevant to human health. The age of molecular biology was in large part spawned by the government/academic partnership. The major stimulus for this type of research, of course, was the proposal in 1952 by Watson and Crick of the double helix as the structure of DNA which offered predictions about the mechanisms of mutation and replication. The actual discoveries of the other Nobelists of the genetic research coterie were important, but of even more consequence was the epoch they engendered with their research tools and methodology.

Much of the recent fundamental information gained in the biological sciences has been obtained by the process of reductionism--the exploring of details and the details of details until all the smallest bits of the structure or the smallest parts of the mechanism are exposed to scrutiny. The scientists responsible for our evolving understanding of biological systems know that the reductionist approach must often precede reconstitutive endeavors. Scientific progress rests on myriads of small observations, tedious measurements, and the findings of investigators asking humble, answerable questions. Instead of reaching for the whole truth, the scientist examines small, defined and clearly separable phenomena.

This approach has had a profound effect upon research that is not frequently perceived. It has blurred the lines between the once sacrosanct territories of the biomedical disciplines. There has been a convergence of biochemistry, genetics, virology, microbiology, physiology, and anatomy; the common language is chemistry.

Watson and Crick's hypothesis for the organization of DNA has had an effect in biology that has been compared with that of the theory of relativity in physics. In the biological realm, not since Harvey's description of the circulation of the blood has such a scientific stimulus been provided. Suddenly, questions which earlier seemed unapproachable were being reconsidered, and new questions that could not have been asked before could now be posed. Now, thanks to that stimulus, to the availability of research tools and metholologies and to a cadre of scientists capable of taking up the challenge, we know much about how genes are replicated; how they maintain extraordinary fidelity, but occasionally mutate; how they are transcribed into RNA and are expressed as protein sequences; and how they expand in number as more complex organizations evolve.

This biological revolution is far from over and, in fact, is beginning to approach major questions with immediate relevance to human health. The burgeoning work on oncogenes, for example, is drawing us closer to an understanding of how carcinogens, cocarcinogens, and host factors may affect genetic apparatus in causing all types of cancers. The remarkable explosion in knowledge about globin gene structure and function provided by molecular biological recombinant DNA technology has offered a unique opportunity to understand disease mechanisms and to develop novel approaches to therapy. Extension of the techniques of molecular cloning, restriction endonuclease mapping, and DNA sequencing promises the solution to both molecular mechanism and prenatal diagnosis of many genetic diseases.

Because many of the understandings gained from the age of molecular biology are now beginning to move toward clinical application, it is obvious that we will need a steady supply of well-trained physician/scientists to help in the incorporation of this new knowledge into the working motifs of medicine. This is a most exciting type of research requiring someone who is both medically knowledgeable and scientifically trained.

But given the rapid pace of advancement in research, the task of keeping abreast is growing more and more difficult for clinicians. Science has become complex, the methods intricate, and the required training long. The explosion of biomedical knowledge in the past decade has forced the progressive professionalization of biomedical research, in particular clinical research. I hope there will always

be room for the creative amateur in clinical investigation but recent history indicates that such a person is less and less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training in the information concepts and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

The importance of more and better quality training for our future physician/scientist cannot be overemphasized. Recent analysis by NIH has indicated that for M.D. postdoctoral trainees, the longer they have trained, the more likely they are to apply for and receive an NIH research grant; unless they have a minimum of three years in research training, they usually are not successful in competing for grants. The most successful applicants of all are those with combined M.D./ Ph.D. degrees. Their success rates are higher than those with the Ph.D. degree and much higher than those with the M.D. degree chiefly, in the latter case I believe, because of inadequate research training. For example, we have found that in programs where the median length of research training is only 12 months, only 20 percent of the M.D. graduates apply for grants and only 10 percent are successful.

There is a great deal of interest in this country--expressed by the Administration, by the Congress, and by the scientific community--in finding means to provide for future clinical investigators. For its part, the NIH has an array of training and career development programs that are especially designed with M.D.s in mind. Because we are convinced that early exposure to research is an important factor in attracting bright and dedicated students into biomedical research, we have set up a number of programs whereby students can supplement their medical education with research experience. For young physicians who are willing to make a major commitment to research, we have developed a new program, the Physician/Scientist Program, which provides five-years of support, including three years of training in basic research and an additional two years in a clinical setting.

Another new program, a cooperative effort of NIH and the Howard Hughes Medical Institute (HHMI), will offer approximately 30 medical students a year opportunity to try research after their second year in medical school. They will be chosen competitively from the Nation's medical schools to spend six months to a year of research training on the NIH campus under the guidance of leading NIH scientists. HHMI will support this program at a cost of about $10.5 million for the first five years to include stipends, travel and miscellaneous support for the students, and for building renovation and construction, for residential quarters, classrooms and teaching laboratories. Recruitment began this fall with the first group of students scheduled to enter the program in the fall of 1985. Although these two programs

are just beginning, it is expected that early exposure to the excitement and intellectual challenge of research will encourage more medical students to undertake careers in biomedical research and that the programs will help to insure a supply of physician/investigators to participate in the "new scientific era."

The importance of scientific training to the small proportion of medical students who will make careers of research is obvious, but what about the vast majority who will practice medicine?

Since medicine is derived from a number of sciences relevant to the health of individuals or groups, physicians must be scientists to utilize these complex disciplines effectively. To be a scientist, the physician must have more than rote scientific knowledge or even fluency in its particular jargon. Physicians must be conversant with the processes of scientific inquiry; how data are obtained and evaluated; how hypotheses are framed, modified, or discarded; and the uses and limitations of inductive reasoning. In short, they must understand science as an intellectual instrument which has been slowly perfected over centuries. Only in this way can they remain attentive to medical progress as a critical and independent participant. Otherwise, they will be in danger of being the passive purveyor of medical fashions. Both the spirit and rigor of science are necessary for the physician to become and to remain a scholar in medicine.

It goes without saying that the state of scientific knowledge at any given time should be one of the factors shaping medical education. Although this has not always been the case, the content of the curriculum of most schools today reflects a reasonably successful attempt to keep up with the times. Because so much is now known about so many subjects of concern to the physician in training, there is an understandable tendency to add to the volume of material that medical students are required to learn. The result can be an increasingly demanding curriculum.

At the annual meeting of the Association of American Medical Colleges this year, the central theme was the report of a distinguished committee on the General Professional Education of the Physician, titled "Physicians for the Twenty-First Century." Without attempting to address the multiple conclusions and recommendations embodied in the panel's report, I wish to call special attention to a recommendation that " . . . basic science and clinical education should be integrated to enhance the learning of key scientific principles and concepts and to promote their application to clinical problem solving." The committee observed that "Although clinical faculties are involved in varying degrees in teaching basic science courses, rarely are basic scientists involved in the general professional education of the physician after the sophomore year."[1] My own

view is that the physician of tomorrow will continue to need a substantial base in science in order to deal intelligently with the technological and intellectual advances of medical practice during his or her lifetime. About one thing we can be certain--namely, that medical education will continue to change.

Over the years, factors other than the state of knowledge have had a strong influence on the structure and operations of medical schools and, at times, have influenced what is taught and how it is taught. It is no revelation, for example, to point out the effect that sources of funding have had on academic institutions--medical schools, in particular.

Some of the deep-seated problems attacked by the Flexnerian reforms in medical education resulted from financing proprietary medical schools from tuitions alone. There was a strong incentive for admission standards and graduation requirements to be tempered to fit the academic qualifications of as many applicants as presented themselves, provided of course they could meet the financial qualifications. Proprietary schools, however, faced steady increases in costs of medical instruction and eventually they recognized the impossibility of meeting expenses from student fees alone. Since they were "for profit" business ventures, these schools could not acquire endowments.

It took the vision and energy of academic statesmen such as Vanderbilt's chancellor, James H. Kirkland, to overcome the shortcomings inherent in the support of medical education through fees alone. His demonstrated devotion to excellence as he rebuilt the Vanderbilt Medical School soon caught the attention of the General Education Board and the Carnegie Foundation. With the support of these public spirited organizations, the necessary steps were taken for development of a model medical school for the south and it became one of the outstanding medical schools of the Nation.

In the first third of this century, large gifts and endowments from boards, foundations, and private philanthropy were responsible for the virtual establishment of some of the great centers of excellence in medical education whose influence continues unabated.

A new shaping force affecting medical education was the emergence in the 1940's of the extramural programs of the National Institutes of Health. When it became apparent that federal support of research in academic institutions would be likely to continue and to grow rapidly, there were some in academic circles who were concerned. They worried

about the possible effect of this new variable on the stability of the educational equation, and of Federal torque on the system that might be exerted through control of choices of research topics.

But the leadership of NIH took care to assure that the new relationship developed as a real partnership. In launching the modern NIH, a key decision was made to rely to an unusual degree upon the advice of nonfederal scientists, especially medical school faculty members. Such outside advisors were made formal participants in policy making for the new institutes through the statutes creating National Advisory Councils for each. Further, the Councils were also made responsible for approving grants by the statutory requirement that no award could be made unless recommended by the Council. This legally prescribed structure for using outside advisors was enhanced immeasurably by the mechanisms evolved for reviewing the scientific merit of grant proposals--the highly regarded peer review system.

Since the late 1940's, about 22,500 individuals, most of them from the academic community, have served as appointed consultants or advisors to the NIH. Their participation in the development and continuation of NIH programs has been extensive and, from our point of view, has been absolutely essential.

This intimate involvement has served well the common interests of the partners and has strengthened the abilities of each to carry out the totality of its individual mission.

The system of study sections, National Advisory Councils, and other outside advisory bodies, has constituted a protection for academic institutions while playing an indispensable role in evaluating the thousands of proposals considered by the Agency, as well as advising in the launching, development, and conduct of a variety of other research activities.

The NIH has given highest priority to investigator-initiated research projects and, in recent years, has allocated half or more of its total budget to this one funding mechanism. This emphasis on investigator-initiated research assures that at least two-thirds of NIH support for research in the average academic institution is used for projects proposed by institutional faculty and not by the government.

Priority setting for research conducted and supported by the NIH is a translation of the influences from several sources--the Congress, the NIH staff and Advisory Groups, and most of all the individual investigators whose grant applications reflect their view of the current research horizons of promise.

Such pluralism assures that major gaps do not long persist in our coverage of research opportunity. It also protects the academic institutions from government-imposed research priorities.

But what has NIH support really meant directly and indirectly to academic institutions, particularly schools of medicine?

One aspect of the effect can be quantified as dollars awarded for research grants and contracts. Such support has been responsible for expanding and enriching the faculties at the awardee institutions--and for making available at the institution advanced instrumentation and other forms of research and teaching resources. In addition to billions in awards to medical schools over the past 40 years, the NIH has contributed substantially through its intramural fellowships and other training programs to the training and experience of several thousand young health professionals and other scientists. This is an aspect of NIH less widely known than its intramural and extramural research programs.

As you may know, we call the Federal reservation where most of NIH is located a "campus." It is not surprising that we refer to our former fellows, visiting scientists, associates, consultants, and former scientific staff members as alumni. We have located some five to six thousand such alumni. In 1975, we held our first Alumni Reunion and expect to have another in conjunction with our centennial celebration in either 1986 or 1987. Instead of a Homecoming Queen and a football game, we had a convocation at which the principal speaker was Nobel Laureate Arthur Kornberg who had worked at NIH from 1947 to 1952. In talking of his own experiences at NIH and describing the general programs we conducted at the time, he told the alumni that "In the untrammeled atmosphere of well-equipped, well-directed laboratories, hundreds upon hundreds of young M.D.s and Ph.D.s were introduced to professional science. Some remained at NIH. But the majority left to staff research, clinical, and administrative departments throughout the world. Today, they populate and direct the finest university departments of basic medical science and clinical science. Today, they are the clinicians in the leading hospitals. Today, they are the research directors of the foremost pharmaceutical companies. They bring a novel outlook from their training in basic biological and clinical sciences to the lecture hall, laboratory, bedside, and to industry."[2]

NIH has indeed been deeply involved in the career development of large numbers of medical school faculty members through the training opportunities provided by the Agency's intramural programs and through the various training programs we have supported in leading institutions across the Nation. These mutually beneficial activities were

responsible for enriching and in a sense transforming American medical education during the fifties, the sixties, and into the seventies. But by the early 1970's, significant changes affecting the partners began to have an indirect effect on the partnership. Compulsory military service for physicians was ended and, as one result, the recruitment of young M.D.s into the Commissioned Corps of the U.S. Public Health Service waned. Bear in mind that many of the research trainees who rotated through NIH were in the Corps.

At about that time, the NIH research training programs were being seriously questioned by the Office of Management and Budget, as well as the Congress. Ultimately, the training programs were stopped and then restarted under different, more stringent ground rules. While this was happening, medical schools began responding to society's demands for more physicians, particularly family physicians. A new emphasis encouraged by Federal funds was placed on medical school involvement in the community health care scene through the regional medical programs and the area health education centers program. Concurrently, the funding pattern of medical schools was undergoing a significant change. Professional service income from care of patients by faculty, in part from medicare-medicaid programs, became an ever larger item in the medical school income and took the place of NIH-sponsored research as a top item in many school budgets.

All the while, applications for research grants were encountering increasing competition as the NIH award rates came down to around 30 percent, because total funding for the Agency had plateaued at a time when the number of applications was growing explosively.

It is easy to understand how applicants would be discouraged by the heightened uncertainty, how they might seriously question whether there is in fact promise of a career in biomedical research with support from the NIH.

I feel that it is especially important for me to assure you as students in this excellent institution that the Federal commitment to biomedical research is steady and stable. I am happy to report that the 1985 appropriation for the National Institutes of Health represents a substantial (almost 15 percent) increase over the 1984 level. This means that our total appropriation in constant dollars is the highest it has ever been.

But even though this welcome increase in funding will enable us to award a greater number of new and competing grants, the competition for them will continue to increase and, with it, pressures on the applicants as well as the reviewers who must make the difficult judgments on the merit of competing applications.

The NIH currently is exploring options aimed at easing some of the procedural requirements so that, for example, initial grants might be made for longer periods of time than the customary three years. Under the present circumstances, a new investigator must prepare a renewal application 15 to 18 months after starting his project. At the November 19 meeting of the NIH Director's Advisory Committee, we will discuss the pros and cons of making most initial project grants for periods of five years. In addition, we will discuss among other things the possibility of awarding seven-year grants for experienced researchers having a proven record of success.

Such reforms and related modifications, if they can be worked out, would reduce to some degree the time and effort required of the investigators as well as the nonfederal reviewers. In the history of the National Science Foundation, called "A Patron for Pure Science," the author J. Merton England told of a scientist who was worrying about taking a position at the NSF at its early days. He commented, "Science seems so much simpler than its machinery." This seems to be true in a time when research studies themselves also are growing increasingly complex. This trend to complexity is swinging the pendulum of research from little science to big science, from the smaller centers to the centers of excellence in education and research, such as Vanderbilt. It is in such centers that a strong need exists to acquaint leading students with the rewards of research as a professional way of life. The motto of AOA, "To Be Worthy To Serve The Suffering," encompasses in its definition of service both clinical care and research.

I would like to close with a paragraph or so from an address given by the dean of Georgetown University's School of Medicine, Dr. John Bernard Henry. He was speaking to the entering freshman class in the fall of 1982. "The laboratory," he said, "seldom seems to beckon with the same drama and excitement as the hospital--but let me assure you it is there. The laboratory and the classroom are the parents of medicine. It could not have been born without them.

"All that this profession is and has become is based on investigation and research. Someone, somewhere, sometime, had an inquiring mind and the intelligence and stick-to-itiveness to labor long hours with one goal in mind: discovery! And it is their discoveries and their accomplishments that enable us to treat our patients and exercise our profession. We would have no knowledge to impart had someone not investigated.

"The clinician receives the gratitude, undying affection, and applause of his patients, but his colleagues know all too well that he has technically put into 'practice' the fruits of someone else's 'labor.' I like to think that makes good sense etymologically, for the words 'practitioner' and 'laboratory' imply practice and labor."[3]

References

[1]"Physicians for the Twenty-First Century," Association of American Medical Colleges, Washington, D.C., 1984, P. 19.

[2]"NIH, Alma Mater," address by Arthur Kornberg, Stanford University School of Medicine, delivered at NIH First Alumni Reunion, 1975, pp. 7,8.

[3]From an address to the Freshman Class at Georgetown School of Medicine, Dean John Bernard Henry, M.D., Washington Post, October 8, 1982.

BIOMEDICAL RESEARCH POLICY OF THE NIH*

by

James B. Wyngaarden, M.D.**

It is a pleasure to make this visit to the University of Minnesota and take part in the ceremonies honoring Mr. Max Winter and this year's recipients of the research grants made possible through the generosity and the foresightedness of Mr. Winter and the Minnesota Vikings. There have been many dramatic advances against childhood diseases, largely due to accomplishments in research: for example, the treatment of precocious puberty with LHRH analogs; successful organ transplantation; and increased survival rates for childhood cancers. New techniques in recombinant DNA are making possible clinical trials with biosynthetic growth hormone and insulin, which will soon benefit the many children with diabetes and growth retardation.

But these Viking grants will not only serve to improve the health of children--they mean a great deal to the recipients--the new investigators just beginning their first independent research projects, and the more experienced investigators, perhaps changing research directions. Although the Federal government takes large responsibility for support of biomedical research in this country, it is clear that a healthy national research enterprise requires cooperation and contribution from all partners involved--the government, academia, and the private sector.

In his invitation to me, Dr. Michael asked that I speak on the general topic of "the biomedical research policy of the National Institutes of Health." I am happy to address this topic and hope that you will first permit a brief excursion into history. As you may know, the National Institutes of Health will soon observe its one hundredth anniversary. We trace our origins to 1887 to the Hygienic Laboratory set up in the Marine Hospital on Staten Island, New York, to study cholera, yellow fever, and other infectious diseases.

In preparing for the centennial events, we have been delving into the early history of the Institution. It was fascinating to learn, for example, that in addition to their battles against disease, the founding scientists were engaged in a fierce bureaucratic struggle. The two principal contestants were our organizational ancestor, the Marine Hospital Service, and the then newly created National Board of Health. This decisive battle was joined over the construction of a refrigerator ship, but the basic issue was not supremacy of the seas but the more familiar contest for bureaucratic turf. As it turned out, this time of troubles became the birth pains of the National Institutes of Health.

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*Max Winter-Minnesota Viking Lecture,
University of Minnesota in Minneapolis, November 13, 1984.

**Director, National Institutes of Health, Bethesda, MD.

The National Board of Health was created by the Congress in 1879. One of the Board's first moves was to ask for a tenfold increase of its own budget. It proposed to take from the Marine Hospital Service authority over the newly passed quarantine law which established a national framework for collaboration on health measures with states and cities. The legislation creating the new body called upon the Board to frame all rules and regulations to prevent the introduction of contagious diseases into the United States, to gather information on all matters affecting public health and give advice on the subject to the Federal government and the states, and to prepare a plan with assistance of the National Academy of Sciences for a permanent national public health organization.

The urgent attention given to this matter by the Congress reflected public alarm over the yellow fever epidemic of 1878. That fear provided powerful motivation for any action that appeared to have promise. Because yellow fever apparently came into this country on infected ships in the summer and died out with the coming of frost, the National Board of Health became convinced that a refrigerator ship could be used to treat incoming cargo as well as the clothing of crews and passengers, thus killing whatever it was that caused the disease. Within weeks, the Congress appropriated $200,000 to be used by the Secretary of the Treasury for the construction of the ship and provided that the plans were to be approved by the National Board of Health. The Marine Hospital Service chiefs were not particularly enthusiastic about the project or, for that matter, with any of the threatening activities of the Board. In a short time, however, the Board's plans for the refrigerator ship were completed and submitted to the Secretary of the Treasury.

But the Secretary of the Treasury referred the Board's plans to his principal health advisor who was also the supervisory Surgeon General of the Marine Hospital Service, Dr. John B. Hamilton. To make a long story short, the plans for the ship sank slowly from sight under the waves of paper whipped up by strict interpretation of the procurement regulations.

The battle raged on, however, for almost a decade. One last fullscale attack was made on the Marine Hospital Service in early 1888. Friends of the now defunct National Board of Health had successfully lobbied committee approval of a bill to set up a Bureau of Health in the Department of the Interior. The proposed legislation would have stripped from the Marine Hospital Service all of its public health functions but quarantine. In her book, "A Profile of the United States Public Health Service," Bess Furman tells how, even after the committee had voted to report favorably on the bill, Surgeon General Hamilton appeared before the Congress at his own request on February 24, 1888, to oppose the measure. He testified that the Marine Hospital Service was already doing all that the proposed Bureau of Health would be authorized to do.

"But how about research?" the Congressional committee asked.

And Hamilton played his trump card which, Ms. Furman said, "probably saved his Service."

The Surgeon General's ace was his testimony that the Service had already begun to conduct medical research in a small laboratory on Staten Island--and that several hundred dollars had been spent in setting up the laboratory. He revealed that, only a few weeks before, research reports had been published on the work being carried out in the laboratory by an officer in the Service, Dr. Joseph J. Kinyoun, who was named as head of the research facility.

This was the first time a committee of Congress had heard of the National Laboratory of Hygiene which eventually would become the National Institutes of Health.

For the first 50 years of its history, the NIH continued as essentially an independent, freestanding laboratory of limited size. The Nation's response to the challenges of World War II brought about the formation of productive partnerships involving the government with both academic institutions and independent laboratories for the conduct of biomedical research. In response to the sudden need for additional knowledge on how to deal with the health problems of the armed forces, the military had little choice but to turn to established nonfederal laboratories for the conduct of vital studies. By grants and contracts, most American scientists not in the Federal service were mobilized for support of the war effort. The arrangement worked. It worked extremely well. The new partnership greatly accelerated biomedical research and development across the spectrum from the most basic studies to the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

My personal association with NIH goes back to 1951, when I joined the National Heart Institute in a position that, as far as I knew, had no name. Now I would be called a clinical associate or a clinical staff fellow. At that time, Dr. James A. Shannon was Associate Director in Charge of Research in the Heart Institute. When he became Director of NIH in 1955, its total budget was $82 million. When he retired as Director, 13 years later, the NIH budget had passed $1 billion.

During Dr. Shannon's tenure, the basic mechanisms of support of biomedical science were established, and these have continued to serve us well. Jim Shannon insisted that Congressional mandates to conduct research in cancer, heart disease, and arthritis, for example, be interpreted broadly. He realized that the science base did not exist to permit a frontal assault on the diseases themselves. He set about building the research capability of this country, both through the intramural program at NIH in Bethesda and through substantial expansion of the mechanism of grants-in-aid to institutions. Corollary objectives included strengthening the institutions in which biomedical research would be done, and development of training mechanisms that would ensure a continuing supply of competent scientists drawn from the best and brightest young people in the universities. Together with Hill-Burton money for clinical facilities, NIH construction funds for research facilities modified the topography of the academic medical center, indirectly changing--and greatly strengthening--medical education.

NIH has proceeded on a course that, in many ways, was charted by a report written in 1945 by Vannevar Bush, the President's Science Advisor, which greatly influenced Congressional action in the immediately succeeding years. This report, Science--The Endless Frontier, outlined policies for Federal support of health research that have served the national interests so well since that time. The flavor and substance of the document stand up in sturdy perspective when viewed with the critical hindsight of nearly 40 years. I would like to read a few sentences from it:

"The publicity and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge. . .

"While additional physicians, hospitals and health programs are needed, their full usefulness cannot be attained unless we enlarge our knowledge of the human organism and the nature of disease. Any extension of medical facilities must be accompanied by an expansion of medical training and research."

Thus, back in 1945, Vannevar Bush laid the groundwork for the Federal government-academia partnership in the pursuit of excellence in biomedical science. And that partnership, over the years, has succeeded. Support of biomedical science during the past three decades, chiefly by NIH, has transformed our knowledge and understanding of biology. The transformation has been so dramatic, so pervasive, that it justifies the use of the overworked term "revolution." Never in the history of biological science has there been so much exciting work going on, so many promising leads in so many fields, or such an army of brilliant scientists at work in their laboratories or at their blackboards. Molecular biology, which began in the 1950s as an exhilarating intellectual adventure in bacterial genetics, with no predictable public benefit, through recombinant DNA technology has permeated all branches of biological science. Human insulin, interferons, and human growth hormones are being produced by bacteria. Agricultural scientists are exploring how nitrogen fixation genes can be insinuated into wheat and rice. The discovery of oncogenes has provided a new paradigm for cancer research. In immunology, the once obscure flocculations and precipitations of test-tube scientists have given us a wholly new insight into a range of human diseases and, in the instance of monoclonal antibodies, provided us a tool whose power is yet to be fully exploited in terms of targeted chemotherapy, and even fertility control. These are impressive examples of the social utility of basic science, and also of the patience needed for the practical development of beneficial measures based upon discovery of new fundamental knowledge.

But how shall we make sure that the momentum of scientific discovery is maintained? The period of explosive growth of the fifties and sixties, when the NIH budget increased twentyfold in constant dollars in 13 years, is long over. The second-stage rocket of the cancer, heart disease, and stroke initiative has now played out. After reaching an all-time high in constant dollars in 1979, the NIH budget leveled off. NIH had become a mature agency competing with other Federal programs for its share of the budget.

In view of these budget contraints, NIH and its partners in biomedical science made a number of painful adjustments to secure the greatest possible amount of the best science within the available resources. Because it did not seem possible to continue all the efforts and programs we had come so passionately to cherish, NIH had to begin to set its research priorities more selectively, taking into consideration a wide variety of factors: the overall mission of the NIH to support research in pursuit of health; scientific considerations; and specific public mandates and assignments as expressed by the Congress and the Administration. Whatever our priorities and programs--which may vary as conditions and opportunities warrant--there are certain abiding principles that have continued to guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over disease and suffering.

Clearly, support of basic research is a responsibility of government. This tenet has been explicitly reaffirmed by the current Administration. The President's budget package for the Fiscal Year 1985 budget contained a discussion of the importance of basic research. It read:

"The 1985 budget reflects the high priority which this Administration continues to give to the support of basic research across all scientific disciplines. Additional support for basic research is based on the premise that the long-term economic strength of the Nation and continued improvement in the well-being of its citizens requires a sustained investment in basic scientific research. . . In addition, support for basic research at universities provides the foundation for the education of future scientists and engineers."

Another guiding principle is our reliance upon our partners in research--the academic institutions. In 1983, for example, 76 percent of health R&D funds used by universities came from the Federal government; 21 percent from university, state, local and other nonprofit sources; and only 3 percent from industry. During most of the history of the NIH, certainly for the past 10 to 15 years, about four-fifths of the Agency's budget has been expended in grants and contracts awarded to other institutions for the support of research. A large portion of that support goes to academic health centers such as the University of Minnesota for the compelling reason that you have a national resource for which there is no substitute--your faculties of trained basic and clinical scientists. And further, one of your central purposes is to ensure the continuing renewal of that precious resource--the trained investigator. In fact, with the increasing complexity of contemporary science, it seems likely that we will tend to move toward more support of the large centers of excellence in science. Minnesota is one such center of excellence--in 1983, it received awards totaling nearly $50 million from the NIH in support of almost 400 separate projects, including research grants, contracts, individual fellowships, and institutional training awards. This gives it a ranking of 13 among all domestic institutions in amount of funds from the NIH.

A third fundamental principle guiding the NIH is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds for the most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period.

The fourth principle is the need to assure a continuing supply of well-trained scientists to carry out the research to meet national health goals. There is a close interrelationship between research productivity and the availability and replenishment of the supply of qualified investigators.

A final basic tenet is that of accountability--by the government and by the recipients of government support. From its outset, NIH took care to assure that the new relationships between the government and academia developed as a real partnership. A key decision was made early on to rely to an unusual degree upon the advice of nonfederal scientists, especially medical school faculty members. Such outside advisors were made formal participants in policy making for the new institutions through the creation of National Advisory Councils for each. Further, the Councils were also made responsible for approving grants by the requirement that no award could be made unless recommended by the Council. This formal statutory structure for using outside advisors was more than matched by the mechanisms evolved for reviewing the scientific merit of grant proposals--the highly regarded peer review system.

Since the late 1940's, about 22,500 individuals, most of them from the academic community, have served as appointed consultants or advisors to the NIH. Their participation in the development and continuation of NIH programs has been extensive and, from our point of view, has been essential.

This intimate involvement has served well the common interests of the partners and has strengthened rather than weakened the abilities of each to carry out the remaining portions of its individual mission.

Thus, the system of study sections, National Advisory Councils, and other outside advisory bodies, has constituted a protection for academic institutions while playing an indispensable role in evaluating the thousands of proposals considered by the Agency.

How well has the partnership worked in maintaining the research enterprise, and what can be foretold about the future? What are the stresses on the system? What are the immediate concerns and the long-term problems?

The NIH had been experiencing an essentially level budget since about 1969. One difficulty is that existing commitments from award decisions of previous years have restricted flexibility in making new awards. A policy termed stabilization, in which investigator-initiated research projects and

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research training have been given top priorities, has been an important factor in budget development since it was articulated in 1980. In order to stabilize essential research programs, and to reduce the turbulence of the system, NIH has endeavored each year to fund a minimum of 5,000 new and competing renewal awards, and to support a minimum of 10,000 trainees.

This stabilization policy makes a powerful statement to the extramural community. It says that NIH is doing its utmost, consistent with program balance and Congressional mandates and directives, to assure that the best research will be adequately funded, and that young scientists will have opportunities in research; that we will protect their entry into the research enterprise, not out of charity but because the vitality of the enterprise--the success of the research endeavor--depends on them.

Without an appreciation of the sociology of science, one might question the wisdom of making the investigator-initiated grant project the keystone of a national research effort. In using this mechanism, we are utterly dependent upon the voluntary submission by individual scientists of new research ideas. In one sense, it is the free enterprise system taken to the extreme. The NIH has little or no control over the range or nature of the ideas submitted to it for possible funding. Yet, this very lack of control is the source of the Agency's ability to tap the best ideas of the best minds in the Nation.

Certainly, no one scientist, no matter how sophisticated or experienced, nor any panel of distinguished scientists, could have the insight and creative ability to produce the array of research proposals submitted to the NIH.

The question might be asked, "If the investigator-initiated grant is so productive, why doesn't NIH devote all of its funds available for extramural research to that mechanism?" The answer is that a number of vital research activities require other mechanisms; for example, large clinical trials. Usually these trials are conducted simultaneously at a number of centers spread across the country. To assure comparability and validity of the findings coming from the various sources, it is necessary that a uniform protocol be rigidly followed at each of the centers. In this instance, creative variations from the agreed upon research plan would be destructive. So the usual mechanism for the support of clinical trials is a contract. Specialized and comprehensive centers represent another mechanism for accomplishing NIH's purposes. Such centers support research on the causes, prevention, and treatment of specific diseases, and demonstration of new methods of treatment.

As an outcome of the stabilization policy, the proportion of the NIH budget assigned to support investigator-initiated research projects has grown from 39 to about 53 percent in 1984, but other mechanisms have been curtailed, especially contracts, centers, and clinical trials. After several turns of the ratchet, many Institute Directors feel that further shifts would seriously limit their abilities to meet other program goals and to maintain program balance.

Fortunately, the new budget--the Fiscal Year 1985 budget--will go far in alleviating some of the stress on the system. The 1985 budget for the NIH is for $5.1 billion, an increase of $699 million or about 15 percent over the 1984 budget. We estimate that this will permit the funding of 6,500 new and competing project grants. The percentage of total NIH funds devoted to research projects will remain at 53 percent. The budget also includes $217.5 million for research training, up 31 percent. We plan to use the bulk of the new money for major increases in trainee stipends, which have become uncompetitive with the stipends offered by other government science agencies and, in the case of physicians, with house staff salaries.

To this point I have outlined the fundamentals of our approach to the support of medical research and to the policy of stabilization. I would now like to raise a subject of special concern; namely, the present and future state of clinical research.

This biological revolution spawned over our 40-year-long partnership is far from over and, in fact, is beginning to approach major questions with immediate relevance to human health. The burgeoning work on oncogenes, for example, is drawing us closer to an understanding of how carcinogens, cocarcinogens, and host factors may affect genetic apparatus in causing all types of cancers. The remarkable explosion in knowledge about globin gene structure and function provided by molecular biological recombinant DNA technology has offered a unique opportunity to understand disease mechanisms and to develop novel approaches to therapy. Extension of the techniques of molecular cloning, restriction endonuclease mapping, and DNA sequencing promises the solution to both molecular mechanism and prenatal diagnosis of many genetic diseases.

Because many of the understandings gained from the age of molecular biology are now beginning to move toward clinical application, it is obvious that we will need a steady supply of well-trained physician/scientists to help in the incorporation of this new knowledge into the working motifs of medicine. Nevertheless, diminishing members of physicians are interested in applying themselves to the clinical research needs of tomorrow.

Given the rapid pace of advancement in research, the task of keeping abreast is growing more and more difficult for clinicians. Science has become complex, the methods intricate, and the required training long. The explosion of biomedical knowledge in the past decade has forced the progressive professionalization of biomedical research, in particular clinical research. I hope there will always be room for the creative amateur in clinical investigation but recent history indicates that such a person is less and less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent upon substantial training in the concepts and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

The importance of more and better quality training for our future physician/scientist cannot be overemphasized. Recent analysis by NIH has indicated that as far as M.D. postdoctoral trainees are concerned, the longer they have trained, the more likely they are to apply for and receive an NIH research grant. Unless they have a minimum of three years in research training, they usually are not successful in competing for grants. The most successful applicants of all are those with combined M.D./Ph.D. degrees. Their success rates are higher than those with the Ph.D. degree and much higher than those with the M.D. degree. M.D.'s have fallen behind chiefly, I believe, because of inadequate research training. For example, we have found that in programs where the median length of training is only 12 months, only 20 percent of the M.D. graduates apply for grants and only 10 percent are successful.

There is a great deal of interest in this country--expressed by the Administration, by the Congress, and by the scientific community--in finding means to provide for future clinical investigators. For its part, the NIH has an array of training and career development programs that are especially designed with M.D.'s in mind. Because we are convinced that early exposure to research is an important factor in attracting bright and dedicated students into biomedical research, we have set up a number of programs whereby students can supplement their medical education with short-term research experience. For young physicians who are willing to make a major commitment to research, we have developed a new program, the Physician/ Scientist Program, which provides five years of support, including three years of training in basic research and an additional two years in a clinical setting.

Another new program, a cooperative effort of NIH and the Howard Hughes Medical Institute (HHMI), will offer approximately 30 medical students a year opportunity to try research after their second year in medical school. They will be chosen competitively from the Nation's medical schools to spend six months to a year of research training on the NIH campus under the guidance of leading NIH scientists. HHMI will support this program at a cost of about $10.5 million for the first five years to include stipends, travel and miscellaneous support for the students, and for building renovation and construction, for residential quarters, classrooms and teaching laboratories. Recruitment will begin this fall with the first group of students entering the program in the fall of 1985. Although these two programs are just beginning, it is expected that early exposure to the excitement and intellectual challenge of research will encourage more medical students to undertake careers in biomedical research and that the programs will help to insure a supply of physician/investigators to participate in the "new scientific era."

In another effort to enhance research training for M.D.'s, NIH is attempting to make training grants to clinical departments more efficient. We will soon advise all program directors that we are reemphasizing certain elements of the guidelines to enforce our conviction that all postdoctoral trainee physicians need longer periods of training. We would like all such trainees to commit themselves to an initial minimum of two years of research training, of which not less than 80 percent of time is devoted to research.

In addition, the guidelines will also stress a stronger basic science component. As a result, it is hoped that M.D.'s will become more successful competitors for research grants.

There are some additional matters concerning the scientific community that we are continuing to examine and approach. For example, we are thinking seriously of possible ways for improving the processes by which applications for funds are made and received. Can we maintain the integrity of peer review and yet require less specificity in grant applications? Can we lengthen the average term of first-time grants so that new principal investigators will not find it necessary to make application for renewal of their grant when it is 18 months old or less? For obvious reasons, we feel that first-time investigators are a highly important category of researcher who must be adequately supported. At the other end of the grantee spectrum is the outstanding and established investigator for whom a mechanism is needed for providing longer term, more flexible support. These and other questions related to grant mechanisms are under discussion at the NIH, and will become the principal item on the agenda later this month of the meeting of the Director's Advisory Committee.

Another matter requiring attention is the need to replace the old and acquire the new increasingly sophisticated instruments needed for today's research. It is estimated that 20 million dollars a year for five years is needed for the purchase of large-scale shared instrumentation resources, with additional funds for the purchase through research grants of the smaller instruments. The NIH is participating in a study by the National Science Foundation to secure a valid current assessment of national need.

Finally, extramural laboratories and facilities are slowly deteriorating. With the exception of funds from the Cancer Program and recently from the National Eye Institute, NIH has not supported the construction of facilities since 1969 and now lacks the legal authority to do so. As a result, many of the facilities built in part from the major NIH construction effort--the Health Research Facilities Program--are more than 20 years old or are rapidly approaching that mark. We believe that a realistic aim of any new federal construction program should be less ambitious, perhaps, than the previous one. It should, however, include new construction to replace outmoded facilities, to relieve overcrowding, to accommodate changing research requirements, including facilities for toxic wastes, for laboratory animals, and for major renovation and repair. Good information on construction needs is sparse, and a current study similar to that being conducted on instrumentation deficits is seriously needed.

Our past history of cooperation with the nonfederal scientific community in the evolution of our Nation's great biomedical research enterprise gives me confidence in our ability to solve current problems through working together. While we all encourage the intense competition that drives scientific discovery, we should view ourselves as collaborators in the operation of the system that supports the research efforts. We are vitally concerned for the health and stability of the institutions in which so much of the essential research is conducted, just as they are for the success of the NIH. The enlightened Federal policy on biomedical research in this country has been unusually successful. Government and the

scientific community have formed a strong and healthy partnership based on long-standing principles of cooperation in the cause of science, and the strength of this partnership will serve us well in arriving at mutually satisfactory and productive solutions to the problems we both face. We share objectives of the highest merit; namely, the conquest of disease and better health for all.

REMARKS*

by

James B. Wyngaarden, M.D.**

Earlier this month we heard quite a bit about the end of a campaign conducted every fourth year. Today we are launching the fourth year of a campaign conducted annually. I am honored to have been asked to join with the National Foundation for Infectious Diseases in reminding the nation's practicing physicians as well as the general public about the importance of adult immunization, emphasizing at this time the uses of vaccines against influenza and pneumococcal pneumonia.

As an aside, I must tell you that it is a special pleasure to be present with Dr. Anthony Fauci on the occasion of his first public appearance as the Director of the National Institute of Allergy and Infectious Diseases. Selection of Institute Directors is one of the most important responsibilities and exacting tasks of the Director of NIH. I can tell you it is done with utmost care; and when a person with Tony Fauci's ability and qualifications is recruited, it is cause for celebration in my office.

In carrying out its mission to uncover new knowledge that will lead to better health for everyone, a primary goal of the National Institutes of Health is to conduct and foster research that could ultimately lead to the prevention of disease. Working toward this long-range objective, each Bureau, Institute, and Division has actively pursued both basic and clinical research that shows promise of leading to methods of preventing or ameliorating disease. In certain instances these goals include finding

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*Presented at the Adult Immunization Campaign Luncheon, National Foundation for Infectious Diseases, November 21, 1984, Washington, D.C.

**Director, National Institutes of Health, Bethesda, Maryland.

methods to detect disease before it becomes manifest; in other instances the aim is to halt or reverse further development of existing diseases. New and exciting prevention research findings are forthcoming from such diverse fields as biochemical epidemiology, nutrition, enzymology, developmental embryology, biochemistry, physiology, immunology, pharmacology, and many other areas. Progress in basic science has reached the point where we now have the knowledge to apply these findings at both the pre-intervention and intervention levels, so that health practitioners and the public can take measures to reduce risk and morbidity associated with acute and chronic disseases as never before. Among the strongest weapons are vaccines.

Since the mid-1960s, the National Institute of Allergy and Infectious Diseases has led the NIH effort to develop vaccines for the control of infectious diseases. Currently more than 50 different antigens are being investigated in NIAID's Vaccine Development Program. Dr. Fauci will discuss in some detail various exciting activities taking place in vaccine development, as, for example, the emergence of new knowledge: recombinant DNA and hybridoma technologies, new findings of how the immune system works, and biosynthetic technologies. Use of such new technologies and new insights promises to allow the development of new vaccines and to accelerate their development.

But no matter how sophisticated our techniques and advanced our vaccines may be, their value is determined by their use. That is why it is so important for groups such as the National Foundation for Infectious Diseases to remind all concerned of the vital role of preventive medicine and of the substantial improvement in American health that is possible through just <u>using</u> the vaccines that are now available. The potential for marked advance in the public health is especially promising through the simple device of encouraging vaccine protection for adults.

To illustrate this fact, one need only cite the recent estimate by the Centers for Disease Control that only 20 percent of the

groups defined as high risk on the basis of medical condition or age received influenza vaccine in any given year.*

A few months ago the CDC released new guidelines on adult immunization developed by its advisory committee on immunization practices. The guidelines will be followed in December by the release from the American College of Physicians of recommendations of its Committee on Immunization. From these two sources, as many as 225,000 copies of adult immunization guidelines will be available for distribution to the public and private sectors of the health care community.

The information office of the National Institute of Allergy and Infectious Diseases is developing ways to assist the American College of Physicians in disseminating its guidelines to the private sector. They will also coordinate with the Centers for Disease Control in their adult immunization outreach activities. This will be a part of an effort to increase awareness among physicians and the public of the need for adult immunization, particularly in the case of the under-utilized pneumococcal and influenza vaccines. After initial distribution of the guidelines to private practitioners and other health professionals has taken place, the next step will be to encourage activities to promote the actual use of the guidelines in preventive health care. In addition, the NIAID also suggests that public education activities be carried out in the fall of 1985 in order to increase interest in and acceptance of the need for adult immunization on the part of high-risk groups.

Our interest in this issue stems from the recognition that if vaccine development is to be successful in protecting against infectious disease, physicians and the public alike must recognize the necessity of adult immunization. In addition, all concerned must be informed about the availability, efficacy, and safety of specific vaccines.

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*Annals of Internal Medicine, August 1984, p. 220.

It is well recognized that many physicians who treat adults do not routinely question their patients about their immunization history. This lack of awareness by physicians of their patients' immunization status is often coupled with a lack of knowlege or acceptance of newly developed and improved vaccines. Physicians have been slow to recommend the pneumococcal vaccines for high-risk patients for a variety of reasons. The ACP and the CDC guidelines will inform practitioners about current data on the efficacy of new vaccines, indications and contraindications for their use, and what, if any, adverse events might be anticipated.

The first step toward adoption of these guidelines by the private sector is to put them into the hands of the practicing physician, particularly those in general practice, internal medicine, pediatrics, and geriatrics. These physicians have need to know that new guidelines exist and can be obtained through the ACP and the CDC. These physicians can be reached through campaigns such as that being launched here, through professional societies and associations, state and local medical societies, and medical journals.

It will be necessary to gain physician acceptance of the procedures suggested so that they are followed in the course of normal practice. Initial efforts to change behavior regarding immunization might be most effective if they are directed toward those physicians who are opinion leaders and who serve as credible sources of information for their colleagues. This would be particularly important in accelerating the acceptance of new or improved vaccines.

Activities such as the one you begin today, and the publication of the guidelines, will almost certainly stimulate editorials and articles in medical journals, and provide subject material for seminars, workshops, and continuing medical education courses sponsored by local medical societies and hospitals.

There are other target audiences, such as corporate medical directors, military medical personnel, nurses and allied health professionals, all of whom need to be aware of the importance of adult immunization..

Launching this campaign and initiation of practical steps for securing more general use of existing vaccines could be regarded as frontline tactics in the war on disease. But in using immunization as a major weapon in this classic conflict, activities behind the lines take on critical importance. For most vaccines are not developed once and for all, but require continual updating, modification, and improvement. Their targets often are in a state of change. Certainly this is true of influenza. Some can remember when it was thought, erroneously, that there was no longer need for a vaccine against pneumococcal pneumonia because penicillin supplied the complete answer.

In this context we should note that, to an unusual degree, the availability of effective vaccines for general use depends upon the willingness of pharmaceutical manufacturers to take financial risks. Each element, however, of the team consisting of the scientist, the manufacturer, and the practitioner is essential to the success of immunization programs.

I can assure you of the deep interest and commitment of the biomedical research community as a whole in making this partnership work.

In prevention of disease through immunization, we reach the fulfillment of the use of medical technology--the solution to the expensive dilemmas so eloquently described by Lewis Thomas in his essays on "halfway technology."

We have in immunization what a mathematician would call an elegant solution--not only the optimum treatment of a disease by preventing it, but also through the use of a simple, relatively inexpensive means that is almost universally available.

INTRODUCTORY REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

Ladies and Gentlemen, it is my pleasure to welcome all of you to the NIH Lecture. The NIH Lecture series was established in 1953 to recognize outstanding scientific accomplishment and to contribute in a vital way to interchange of scientific information. Tonight's lecture will be presented by Dr. Richard Axel, Acting Director, Institute of Cancer Research, Columbia University.

Dr. Axel will share with us his work on genetic control of innate behavior, using the Mollusk Model Aplysia. Aplysia is a shell-less marine snail that can weigh as much as five to ten pounds. Using recombinant DNA techniques, Dr. Axel has defined a family of genes encoding a set of neuropeptides whose coordinated release governs a fixed-action pattern: egg laying.

Dr. Axel started his research career as an undergraduate at Columbia University, where he earned an A.B. degree Magna Cum Laude in 1967. In 1970 he earned an M.D. degree from the Johns Hopkins School of Medicine, followed by an internship and fellowship at Columbia University.

In 1972 he served as research associate in the laboratory of Dr. Gary Felsenfeld, NIADDK, where he worked on the structure of globin genes in chromatin.

In 1974 Dr. Axel returned to Columbia University as assistant professor, Department of Pathology, Institute of Cancer Research, becoming professor four years later. He became acting director of the Institute of Cancer Research in 1983, the position he holds today.

Dr. Axel also serves as the Higgins Professor of Biochemistry and Pathology, and Professor, Howard Hughes Medical Institute.

Dr. Axel is the recipient of several awards, including the Eli Lilly Award, the Alan T. Waterman Award, and the Passano Foundation Young Scientist Award, and has been invited to deliver the Harvey Lecture at Rockefeller University, and University Lecture at Columbia University. Last year he was elected to membership in the National Academy of Sciences and the American Academy of Arts and Sciences.

His service to the scientific community includes positions as associate editor of Cell, and chairman of the Molecular Biology Study Section, NIH.

Please join me in welcoming Dr. Axel to this NIH lecture.

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*Remarks presented at the NIH Lecture, Masur Auditorium, National Institutes of Health, Bethesda, Maryland, November 28, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

THE PRIORITY OF PATIENT-ORIENTED RESEARCH FOR THE NIH*

by

James B. Wyngaarden, M.D.**

I am very happy to be here today to talk about some matters that confront us all, the present and future status of clinical investigation. I am personally very supportive of the role that the General Clinical Research Centers (GCRC) have played. I know what value they can have to a department of medicine from my years at Duke, having used it and having watched others use it there. Last year I had the opportunity to participate in the 20th anniversary celebration of the GCRC in Mount Sinai Hospital, and just this past September I spoke at the dedication of the outpatient clinic at the Dallas Southwestern GCRC. Both of those occasions offered a chance to learn about the accomplishments of those individual centers and their concerns and the challenges that they face.

As many of you know, there's a strong commitment on the part of NIH to continue to support patient-oriented research across the entire spectrum, from basic science to development of new knowledge to its clinical application. At every opportunity, we try to demonstrate to the Congress and to the Administration the importance of continuing support for clinical research in its broadest definition. In public statements, we try to make clear that the biological revolution spawned some forty years ago, largely through NIH support for basic research, is beginning to approach major questions with immediate relevance to human health. The burgeoning work on oncogenes, for example, is drawing us closer to an understanding of how carcinogens, cocarcinogens, and host factors may affect the genetic apparatus causing, perhaps, all types of cancer. The remarkable explosion about globin gene structure and function provided by the recombinant DNA technology offers a unique example of understanding disease mechanisms and perhaps offering opportunities for novel approaches to therapy. Extension of these techniques of molecular cloning, restriction endonuclease mapping, and DNA sequencing promises the solution to both molecular mechanisms and prenatal diagnosis of many genetic diseases. We also try to make clear that because many of the understandings gained from the age of molecular biology are now beginning to move toward clinical application, it is obvious that we will need a steady supply of well-trained physician-scientists to help in the incorporation of this new knowledge into the working motifs of medicine.

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*Address Given at the General Clinical Research Centers Program Directors Conference, Scottsdale, Arizona, November 30, 1984.

**Director, National Institutes of Health, Bethesda, Maryland.

We at NIH are also very much aware of the important roles that GCRCs play in the maintenance of the national clinical research effort. The GCRCs support 80 percent of the patient-oriented research for the grant programs of the NIH categorical institutes. The two largest groups of users of the GCRCs, taken as a whole, are investigators supported by grants from the National Heart, Lung, and Blood Institute and the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. This latter institute alone supports some 700 projects that utilize the GCRC facilities, accounting for the heavy concentration of endocrine and metabolic studies at the GCRCs. In national terms, more than 3,500 projects are conducted at the GCRCs each year by a small army of investigators, most of whom receive support from NIH research grants, training grants, program project grants, contracts, or career development awards. I might add that it is a testimony to the importance of the work going on at the GCRCs that many of them have a broad base of support that goes beyond the NIH and other Federal agencies; many projects are funded by the private sector. I think this mix of support is a healthy situation, although it is expected that most of the work will continue to be funded by the NIH project awards.

The GCRCs constitute a unique environment for a very special kind of research--indeed a very special kind of clinical research. Because of its very nature, the GCRC provides an atmosphere where the many paths of inquiry and discovery about life processes, particularly those that stem from efforts to understand and intervene in disease states, can flourish. Almost everyone can appreciate the contributions to human health gained through the "bench to bedside connection." But that is only one possible path to scientific discovery. The GCRC provides a milieu in which the path of inquiry can flow in the opposite direction--"from bedside to bench," thus producing major advances to our understanding of fundamental biological phenomena.

Many have expressed their concerns in recent years about the future of this two-way flow--"bedside to bench" and "bench to bedside." Dr. David A. Hamburg, former President of the Institute of Medicine, put it well in 1980: "We must do everything in our power to see that the great fundamental advances--indeed the inspiring advances in molecular and cellular biology--will be available as soon as possible for health interventions of a demonstrably useful character. But the authentic biological revolution that has been generated by several decades of intensive basic research is not easily translated into clinically valid applications. An interpreter is needed, and it is the clinical investigator who serves that function. The flow of information is by no means unidirectional; if basic science has something to say to clinical investigators, so too does clinical investigation offer much to basic science. Clinical research remains the vital bridge between advances in basic science on the one hand and improvements in health care--diagnostic, therapeutic, or preventive--on the other."

Given the importance of continued clinical research, we are concerned that the percentage of M.D.s holding NIH research grants has progressively fallen over the years. Ph.D.s hold approximately 68 percent of traditional NIH research grants (R01s) while M.D.s hold only about 22 percent. If M.D./Ph.D.s are added to those with M.D. degrees, the percentage held by those with professional doctorates climbs to about 31 percent. Although this figure does not give a full accounting of M.D.s working under NIH support--for

example, it does not capture those M.D.s who are working under program project grants or in centers other than as principal investigator--we are concerned about the possible downturn in the kinds of research that can only be done by those trained in both clinical medicine and in research concepts and methodologies.

The decline in the percentage of M.D. investigators working under R01 grants reflects in part the submission of fewer grant applications by M.D.s than by Ph.D. scientists. Another factor, of course, is the increasingly intense competition. Clinical research applications are more often disapproved by study section reviewers, and particularly those involving human subjects are more often assigned poorer priority scores than are applications in which no human subjects are involved. Approval rates for studies that do not involve human subjects are substantially higher than those for studies with human subjects, regardless of whether the principal investigator is an M.D. or a Ph.D.

There has been a general impression that protocols developed by physicians have suffered at study section review because the reviewers, most of them basic researchers, have a bias toward basic research studies, and fail to understand the continuum that clinical research represents from the most basic studies to clinical application. If this were the case, the problem might be solved simply by bringing in more clinical investigators to add to the review groups. But, at a recent retreat at NIH to examine a number of peer review questions, participants reported the perception that physicians are tougher on their own clinical research colleagues than are the basic researchers. Withal, a general feeling was expressed that, while there may be some improvements needed to strengthen the initial review of clinical applications--and this will receive further scrutiny--the overall peer review system appears to be succeeding in assuring an equitable treatment of applications for patient-oriented research.

Although much information on review of clinical research applications is anecdotal, a study a few years ago by the Division of Research Grants provides some data, with which I know many of you are already familiar.

In order to discover why applications to NIH for grants to conduct clinical research may either be disapproved or receive poor priority scores in the review process, the Division of Research Grants examined 256 applications rated by 13 different study sections. For this study, clinical research was narrowly defined as research involving human subjects that included a doctor-patient relationship. The study showed that investigator qualifications and resources at their institutions played a very minor role in poor rating. Flaws in research design and conception of the hypothesis led to poor scores from reviewers. The most frequent deficiencies--faulty hypotheses and inappropriate experimental design--were the same flaws that were cited in basic research proposals that were disapproved or given low scores.

The facile explanation that there is a greater inherent difficulty in working with human subjects may not be the entire answer to the lower approval rates for physician-investigators. Science has become complex, the methods intricate, and the training period so long that the physician, even after two or three years of fellowship training, remains less well trained than the

Ph.D. scientist who has been training for a research career since the baccalaureate. In my own view, the trends of the past decade reflect the progressive professionalization of biomedical research, in particular clinical research. I personally hope that there will always be room for the creative amateur in clinical investigation, but recent history indicates that such a person is less and less likely to secure external support for his or her work. Success for an M.D. investigator is increasingly dependent on substantial training in the information, concepts, and methodologies of complex modern science. To be a first-rate scientist and a well-qualified physician is a demanding calling.

The importance of more and better quality training for our future physician-scientist cannot be overemphasized. Recent analyses by NIH have indicated that as far as M.D. postdoctoral trainees are concerned, the longer they have trained, the more likely they are to apply for and receive an NIH research grant. Unless they have a minimum of three years of solid research training, they usually are not successful in competing for grants. M.D.s have fallen behind chiefly, I believe, because of inadequate research training. For example, we have found that in programs where the median length of training is only 12 months--and that, incidentally accounts for more than half the people who enter the NIH training programs in clinical settings--only 20 percent of the M.D. graduates ever apply for NIH grants and only 10 percent are successful--10 percent of the total. By contrast, those with 30 months of training or more apply for NIH grants in 43 percent of instances, and well over half of those who apply, or 70 percent of the total, are successful. The rate is far better for M.D. fellows than for trainees; the fellows usually receive longer research training than M.D.s on the institutional training grants.

Given the importance of rather long and rigorous training for clinical researchers, we are also concerned that we have been failing to attract the number of qualified physicians into research training perceived to be desirable. This shortfall of physician-investigators alters the balance between M.D. and Ph.D. scientists deemed essential for coordinated progress in basic science and clinical research.

NIH has devoted considerable attention to the problem of training M.D. researchers and has introduced some major steps toward its solution. At the undergraduate medical student level, we have continued to give the Medical Scientist Training Program (MSTP) top priority in our training portfolio. In the MSTP this past year, we supported about 680 students at 24 schools moving toward a combined M.D.-Ph.D. degree. We regard this 6-year program as one of our most successful in terms of building up clinical research. Seventy percent of the graduates hold positions in academic medicine doing research and engaging in the training of other physicians. The program will be strengthened to support approximately 725 students per year, resulting in production of more than 100 graduates per year of the type of scientists who are currently competing most successfully for R01 research grant support.

The NIH also has a number of programs that provide early exposure to research careers at the student level. This past year, more than 1,100 medical students availed themselves of off-quarter training opportunities supported by NIH. With the new exemption of the first year of NRSA support

from payback obligation, the NIH last year reinstituted the post-sophomore fellowship, or its equivalent, to provide a full year of research training within the medical school experience under an NIH fellowship or traineeship. The NIH also offers summer research experience at Bethesda, and during this past year more than 50 medical students participated in that program.

The physician who has completed four years of medical school and several years of clinical training is, by and large, only modestly, if at all, prepared with research skills. Even where research participation in one or more research projects has taken place, the experience does not substitute for a planned program to develop research expertise. A series of NIH awards, called Career Development Awards, provides research development opportunities to qualified individuals with demonstrated research potential. One mechanism has been particularly successful in the attraction of physicians--the Clinical Investigator Award. It provides for three to five years of supervised research development in areas of immediate interest to the funding institute. It offers up to $40,000 per years in salary plus commensurate fringe benefits and some modest amount of research support. This program has been successful and thus demonstrates a potential for expansion, that is for the opportunity for competing renewals. There were 92 such awards made in 1984.

A new addition to the Career Development Award Series is the "Physician/Scientist Award," designed to provide five years of phased supervised research development. Made primarily as an individual award, these programs are based in departments with established records in producing physician-scientists. The first two to three years must be under the guidance of a sponsor who is a basic scientist. The second phase, undertaken at a more independent level, is intended to provide support during transitional years when the awardee will establish a personal research program. This program is sponsored by eight NIH Institutes. It does not replace current training or fellowship programs and is small in scale, and perhaps will level off at approximately 250 awardees in three years. It complements the MSTP program in providing graduate school level experience for the professional degree holder who begins at a post-medical school stage. In 1984, we made 37 individual awards and 3 program awards for a total of 43 individuals supported.

The GCRC program itself has made a major contribution to training M.D.s in research. The CAP (Clinical Associate Physician) program has produced about 110 graduates, of whom approximately 80 percent have remained in academic medicine. To date, half of these graduates in academic medicine have obtained NIH support for their clinical research investigations. In addition, the GCRC program has for the past five years had a very popular medical student program which provides exposure to clinical research for periods of three to six months.

In the GCRCs, where you have a highly specialized setting with rigid protocols, there are a variety of opportunities for research-oriented nurses also to get training or actually participate in research. Nurses could be involved in research at a variety of levels--in data acquisition that relates to patient care, as apprentices to independent investigators, or as principal investigators or collaborators where patient care is a significant part of the study, and I would encourage all of you to look for ways to incorporate more nurses into the actual research program in your centers.

It is also encouraging to note that the private sector is beginning to participate in programs to support training for clinical investigators, some of which are operated through individual GCRCs.

We at NIH are especially enthusiastic about our newest program to help provide for the future of clinical research--a joint project with the Howard Hughes Medical Institute (HHMI). This will support up to 30 medical students a year on the NIH campus, working with leading NIH intramural scientists for periods of six months to one year. The program is just beginning, but we expect that it plus other major programs will help ensure a supply of future physician-investigators in the years to come.

In another effort to enhance research training for M.D.s, NIH is attempting to make institutional training grants to clinical departments more effective and more efficient. We will soon advise all program directors that we are remphasizing certain elements of the guidelines to enforce our conviction that all postdoctoral trainee physicians need longer periods of training. We would like all such trainees to commit themselves to an initial minimum investment of two years of research training, of which not less than 80 percent of their time should be devoted to research. We're particularly interested in eliminating the ambiguity between training for research and finishing subspecialty clinical training for which many of these grants have been used in the past. In addition, the guidelines will also stress a stronger basic science component and the need for a continuing plan of research development for those trainees who are initially successful and promising, and we would recommend an additional two to three years of research training for such people. As a result, it is hoped that M.D. trainees will become better prepared to compete for research grants of the R01 type.

But the wisdom of undertaking research training could easily be questioned by a young physician if the opportunity to engage in supported research in the future is highly uncertain. One major factor influencing a young physician's decision is his or her perception of the long-term stability of Federal support of research. This is one reason for NIH's continued emphasis on the need to "stabilize" our offering of grants for investigator-initiated project research--to provide a reasonable degree of assurance about future opportunities. The policy of funding a minimum of 5,000 new and competing awards has helped, we believe, to stabilize emerging research careers. This stabilization policy has made a powerful statement to the extramural community. It has said that NIH is doing its utmost, consistent with program balance and congressional mandates and directives, to assure that the best research will be adequately funded, and that young scientists--including clinical researchers--will have opportunities in research; that we will protect their entry into the research enterprise, not out of charity but because the vitality of the enterprise, the success of the research endeavor, depends on them.

Fortunately, the new NIH budget for fiscal year 1985 makes the future of biomedical research, at least in the near term, look even brighter. The 1985 budget for the NIH is for $5.1 billion, an increase of $699 million or about 15 percent over the current budget. We estimate that this will permit the funding of 6,528 new and competing project grants, an all-time high. This would bring the percentage of total NIH funds devoted to research projects to about 53 percent. The budget also includes $217.5 million for research

training; this is an increase of 31 percent from last year. We plan to use the bulk of the new money for major increases in trainee stipends, which have become uncompetitive with the stipends offered by other government science agencies and, in the case of physicians, with house staff salaries.

Before I close, I would like to review briefly a few more developments involving NIH that may be of interest to this group.

As you know, the President vetoed the Health Research Extension Act of 1984, which included as one of its major provisions the creation of two new institutes for the NIH: one for nursing and one for arthritis research. The Administration had opposed the creation of the new institutes and, in fact, most of the provisions of that bill when they were first introduced in the Congress.

The Institute of Medicine made public its report on the organization of NIH. One of its key findings, with which the NIH agrees, is that there should be a presumption against establishing new institutes at NIH and that major structural changes in the NIH should be made sparingly. At the same time, NIH most continue to be alert to changing health needs and emerging scientific opportunities and respond positively to such changes. We are concerned, however, with the possibility that the Health Science Board as proposed in the report might become an additional layer of management.

In other actions, the NIH will soon introduce a formal appeals process for the peer review system beginning on a trial basis early in 1985. It will consist of two steps. First, the principal investigator would communicate informally with the proper Institute or Division and the Division of Research Grants. Then, if satisfaction is not gained, the principal investigator and the applicant institution may appeal formally to the Deputy Director for Extramural Research and Training.

Also, with regard to the NIH Peer Review System, we are thinking seriously of possible ways for improving or fine tuning the processes by which applications for funds are made and received. Some of the questions raised are: Should first-time research grant awards be for longer periods of time--presently about 95 percent of them are for three years--so that new principal investigators will not find it necessary to make re-application when the first award is only 15 to 18 months old? Would a 4- or 5-year standard period of award eliminate some of the "catch 22" features of such short awards? Should well-established investigators receive research grant awards for longer periods of time and should the review process in those cases rely to a greater extent on "track record"--in other words, can we move the process somewhat away from the research procurement mentality back more toward the investment mentality that characterized the system a few years ago? Are there ways to enhance the stability of mid-career investigators? These major questions obviously come with price tags attached to them and, in an essentially steady state budget, if we make moves in that direction, there will have to be some trade-offs. These general questions are very high on our agenda for additional attention this year, and I can assure you that my office, together with my NIH colleagues, will be thinking of additional ways in which we can improve the system of peer review which already has a record of established excellence, but can always be improved even further.

Thank you very much.

QUESTIONS AND ANSWERS

Thank you Dr. Wyngaarden. I'm sure that some of you might have some questions that you might want to address to Dr. Wyngaarden. Could you come up to the microphone so everybody could hear?

Q: I wonder whether this isn't a losing battle that we're fighting. That, on the one hand we have everybody in research wanting to find an idea and then wanting to carry it through so that his name is first on the paper and he's the one who goes to Stockholm eventually if it really comes through. And that's certainly been the spirit of 95 percent of the people I've seen over the years who go into academic medicine to do basic research . . . and on the other hand, we have the reason the battle may be a losing one, I think, where the complexities of the basic research where the idea now has to be worked out and the need to have a clinician who can inject the liver extract into a patient and knows all the problems of doing this needs the training that really precludes the kind of basic training, the kind of training at the bench that could be done 30-40 years ago. Edwin Cohn, who ran the Department of Physical Chemistry at Harvard, used to say, "When I'm with physicians, I put on my Ph.D. hat, and when I'm with Ph.D.s, I put on my M.D. hat"--and he could do it. But I certainly find, even in my laboratory, when we get into what is the frontier of doing meaningful or what we hope is meaningful research, it's--maybe it's because I'm just too old--but I just can't cope with the technicalities of the new chemistry--molecular biology, and at the same time be able to keep up with the skills that can't be taken for granted of a clinician who has to go over to Chip Demmings' GCRC, have a patient in there and be sure that we take care of the patient and to say nothing of getting along with our IRB. I wonder whether this doesn't mean that in the future, really, much as it would be nice to have the physician-scientist awards and the programs develop people who can be the Minots again, or Bannings again, or Addisons, that it really isn't going to be possible anymore, and we're going to have to have what Walter Bauer I guess first set up--the idea of team research and oriented goals and people working at it from the levels of Gerdy Perlman or Fritz Lippman and clinicians on the other side.

A: Although I wouldn't describe it as a losing battle, I do think the style of research as performed by physicians will change. It seems to me that we will continue to need a cadre of investigators who are both medically knowledgeable and scientifically trained. I'm not sure that the group most heavily involved in research will need the extent of clinical training that is required for double board certification. But many departments of medicine have shortened or modified their training programs, and the American Board of Internal Medicine now has introduced more flexibility, to encourage hybrid careers. I think some reductions in length of clinical training must occur if we are to produce well-trained research scientists with medical backgrounds before all one's vigorous years have disappeared. The team concept is clearly growing. In NIH-supported training programs in clinical departments, about 900 of the 2,800 slots are occupied by Ph.D.s who are moving into clinical research for a variety of reasons--part of it is the vacuum that's there to be filled, part of it is the positive attraction, part of it is the competition

in the traditional tenure tract for a Ph.D. scientist. But that development will create a great deal more collaborative work or team approach. And further, I think that departments of medicine will continue to differentiate. The people who are very deeply involved in science simply cannot carry the heavy clinical loads, and departments have to make arrangements to accommodate such people. But I expect that there will be an enhanced rather than a diminished need for well-trained physician-scientists. Those who arrange the finances of academic careers really have to take such divisions of labor into consideration, and maybe not every department of medicine can accommodate to that.

Q: (Dr. Jacobs) I think that many of us view the challenges that are clearly with us already in the terms of the training and the sustaining of clinical investigators with hope and enthusiasm, and many of us look with great favor on the programs you summarized that are new, mounted by the NIH, including the physician-scientist award particularly, as well as the accomplishments of the MSTP program, but wonder whether the graduates of those programs will really be suited temperamentally or by training to fill the roles in the hands-on types of clinical investigation for which the Cuca study was specifically addressed, and about which we have a special concern. I wonder if you would comment on that particular subgroup and ways that you think that cohort can be planted if you will and nurtured, as opposed to the cohort of M.D. clinical investigators who do clinically related bench work or work on samples from patients but perhaps do little hands-on clinical work.

A: I think there must be people at different points on that spectrum. The CAP program is an example of a program deliberately designed to introduce potential medical scientists into research in a clinical environment and in the GCRCs rather specifically, but it too will have its training requirements. The point that I'm really stressing is that the model which worked so well in the 1950s and 1960s of perhaps two years in a clinical research program with research and clinical subspecialty training intermingled may be a model whose time has come and gone, for it has not proved very successful in the last decade; there are, of course, notable exceptions. I think that even in the role of research involving direct patient contact, the training aspect deserves special emphasis. Of course, research of the type that can only be done by a physician, for example involving invasive procedures, may require more than two or three years of general clinical training. I think we need a blend of all of these types of physician-scientists; we will continue to need physicians who utilize their backgrouind in basic science departments, others in clinical departments who do very little clinical work, and still others who divide their time. I think we need to promote all of those careers. The medical student pool is an extraordinary talent pool, and I think we need to do our best to capture those individuals who have creative potentiality in any one of these roles.

Q: (Dr. Glueck of Cincinnati) I'd like just to comment on the point you made about grant procurement. For many of us who have, say, a GRC, a program project, an R01 and a training grant, for example, there is a never-ending treadmill of renewals, reports, reinvestigations, and I would estimate that many successful people with that type of load are carrying 30-40 percent of their time simply in the procurement procedure which diminishes their ability to train, teach, and do research, and so I'd just like to emphasize from my

point of view how crucially important I think it is to focus on that area to try to facilitate perhaps a more MRC-type of situation where you could provide longer term support for those types of very capable investigators.

A: I fully agree, and we're working on that; I would like to simplify the process as much as we can. I took one small step in that direction a couple of years ago when we put a page limit on the application; but we didn't put a page limit on the appendix, and that has grown in size as the body of the application has shrunk. We're addressing this matter again; in fact, we spent several days on this issue this fall. We had a retreat of Institute Directors and invited several eminent scientists to spend an evening with us talking about their experiences and their observations. Then just two weeks ago, we devoted a full day of the Director's Advisory Committee to three major questions about the extramural award system: Could we simplify the system and correct some of its perceived defects and inequalities? Could we stabilize first-term investigators by lengthening the initial period of support? And could we do something for the mid-career, established investigator that would diminish the amount of paper work, such as longer grant periods, and less rigid requirements for detail on the applications? By coincidence, we had a number of interesting letters on the subject that were not timed to this event. One person who had done some reviewing for the British system wrote to say that he'd been impressed how much you really can judge from a 7- to 10-page application compared with the NIH applications, one with far less specification yet one on which he felt he could reach a value judgment. What has happened is that as the competition for research support has increased, applicants have been stimulated to write longer and more detailed applications, and the review process has rather subtly shifted from a search for what's promising in an application to a search for minor defects that will justify cutting the budget, shortening the time, giving a low priority, or rejecting it. Part of that, I suspect, was inevitable given the competition, but part of it was a response to an interest of the Government Accounting Office in 1976 to introduce greater accountability. They asked, for example, whether we shouldn't have annual reviews of all awards. They said, "Last year you funded down to a priority of 240, this year to 190; shouldn't you terminate some of those 240's so you can fund some more 200's and 210's this year?" Well, you can see what a chaotic situation that would create. One of the responses that NIH made in an effort to deflect this criticism was to advise study sections to give shorter awards, and the system responded and the 3-year award became the mode. The average length of time for support is now 3.2 years, an increase of 0.2 of a year in the last 3 years; but 80-90 percent of our awards are for 3 years. As you know, my sentiments are for lengthening the period of the award for several categories of investigations, but that comes with a price tag; for example, if we make all first-time awards to a new investigator for five years, that would increase the commitment base in the fifth year by 260 million dollars over the 1984 base. That's about a 10 percent increase in cost in that category of awards, and if the budget isn't increased, that translates into approximately 10 percent fewer new starts. So you can appreciate that trade-offs have to be considered if we take a step of that sort.

INTRODUCTORY REMARKS*

by

JAMES B. WYNGAARDEN, M.D.**

The roster of distinguished men and women who have delivered NIH lectures since the early 1950's is impressive indeed. It is regrettable that space does not permit us to list on the programs the titles of the presentations that have been made in this series. For, just a glance at the array of subjects would convey a sense of the movement and excitement in the biosciences over the past three decades. From time to time we have heard authoritative presentations from disciplines and activities related to but outside the nominal scope of the NIH scientific mission, and invariably such presentations have had an enthusiastic reception.

I was especially pleased when the recommendation was made that the December 12, 1984 lecture be delivered by the Secretary Emeritus of the Smithsonian Institution, Dr. S. Dillon Ripley.

Dr. Ripley is a scientist among scientists--a biologist, ecologist--and, as an ornithologist, an authority on the birds of the Far East. His selection as the eighth Secretary of the Smithsonian Institution--a post he assumed in 1964--was an event of happy consequence for culture, for science, for the arts, and for education. He has been singularly effective in carrying out the Smithsonian's objective--"the increase and diffusion of knowledge." In his address, Dr. Ripley will tell us of the recent period of remarkable growth of the Smithsonian.

Although there was spectacular addition to as well as expansion and improvement of the Smithsonian's programs and facilities during Dr. Ripley's stewardship, his most lasting mark may well be the result of his influence on the public orientation of the Institution.

He acted on his belief that museums should be, in his words, "points of contact in a life-long process of renewal of the personality, of curiosity of public enlightenment" and that they should be exciting and lively.

Dr. Ripley is a New York City native who from childhood has been fascinated with ornithology and the Far East. At the age of 13, he visited India with his family and, with his older sister, took a six-week walk into western Tibet.

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*NIH Lecture Delivered by S. Dillon Ripley, Secretary Emeritus, Smithsonian Institution, Masur Auditorium, December 12, 1984.

**Director, National Institutes of Health, Bethesda, MD.

He was graduated from St. Paul's School in Concord, New Hampshire, and Yale University where he was a history Major preparing to study law. He decided, however, that he was more interested in ornithology and took up zoological studies at Columbia University, eventually being appointed to a fellowship and teaching assistantship at Harvard University where, in 1943, he received his Ph.D. degree.

After wartime service in Southeast Asia, he joined the staff at Yale where for 18 years he was a member of the faculty and for four years before coming to the Smithsonian, he was Director of Yale University's Peabody Museum of Natural History.

He has led or participated in many research expeditions and field trips into Asia. Since his marriage in 1949, he has been accompanied on six major subsequent expeditions by his wife, Mary Livingston Ripley, who works in the fields of ornithology and entomology.

Dr. Ripley is a prolific writer, has been awarded some 15 honorary degrees, and has been honored by many countries and organizations.

We are honored indeed to have you with us, Dr. Ripley--and look forward to hearing your description of "Twenty Years A'Growing."

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